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OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

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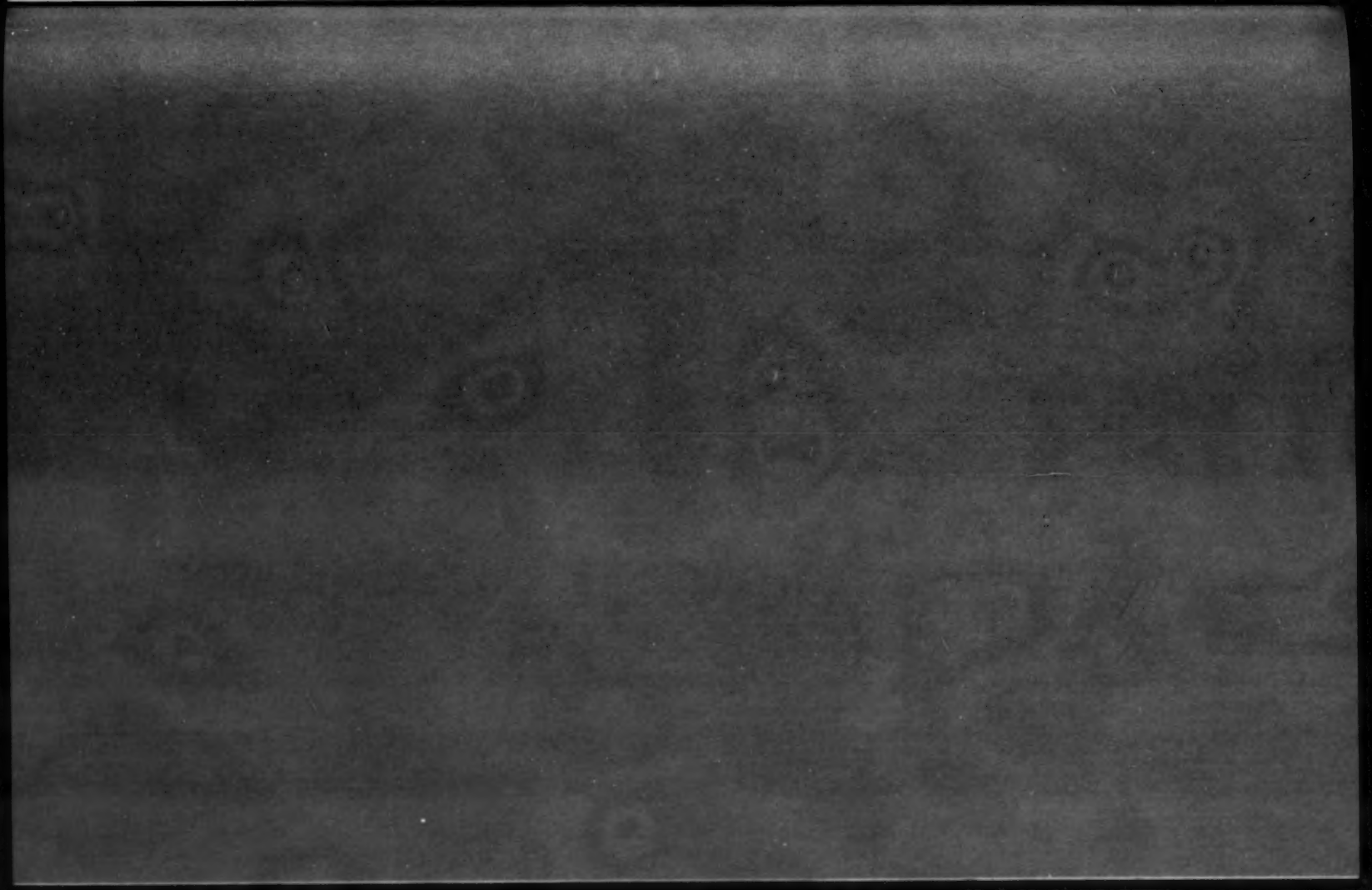

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

FEBRUARY 1941

HUMANISM AND SCIENCE*

ALAN GREGG

Director of the Medical Sciences, The Rockefeller Foundation

The Linsly R. Williams Memorial Lecture

IN VENTURING to link Humanism with Science it is my purpose to direct your attention to an attitude of mind which I hold to be so characteristic, so strongly reminiscent of Linsly Williams that the whole theme of my talk tonight is intended as a tribute to that lovable man.

It is a perilous honor to speak of him to this audience, but happily I can offer in this first Linsly Williams Lecture not merely the initial paragraphs, but the entire substance of the lecture in his memory. I shall devote all of my efforts this evening to presenting a point of view which a scientist—especially a medical scientist might well adopt—a point of view which is rare in mankind and none too common among physicians; so far from common, indeed, that you will detect a certain nostalgic yearning in these remarks, an optative mood, an irrepressible desire that we might see more of it or at least hear more of it among physicians. This point of view, this philosophy, was the frame of refer-

* Given November 14, 1940 at The New York Academy of Medicine as the first lecture of the Lectures to the Laity, Sixth Series.

The New York Academy of Medicine acknowledges with gratitude, the courtesy of the Columbia University Press in permitting the prepublication of Dr. Gregg's address. This essay will be published by the Press in a volume containing the sixth series of Laity Lectures.

ence for one of Linsly Williams' most precious traits. I refer to his rare talent for combining sympathetically and therefore more effectively with a great many different kinds of people for his and their own good and the good of all of us. If you knew him no illustrations are needed to show how endearing can be this talent; and if I were to enumerate the benefits he brought to this Academy of Medicine, to the standards of our profession in this City, to the Public Health of New York, to the accomplishments and status of the National Tuberculosis Association, I should prove that this talent is important. And yet, to describe it as endearing and important does not suffice. The capacity to combine sympathetically with a wide variety of persons is one of many metals lying embedded in the matrix that I attempt to indicate by my title—Humanism and Science.

I offer no apology for reaching into the past and into fields far removed apparently from modern science in order at the outset to place before you what I mean by the word "Humanism." Whenever permitted by circumstances to enjoy the luxury of reflection, man has been drawn repeatedly to thoughts about three types of relationship: his relation to God, his relation to himself and his fellows, and his relation to the world of nature. I have not time for many examples of this triad of civilized preoccupations. Suffice it to note that in Europe by the late Thirteenth Century man's relation to God had become a preoccupation so elaborated and so dominating as to minimize, if not indeed to exclude, reflection upon man's relation to man and to the natural world. Intuitive curiosities had already been trimmed down into dogmatic utterances, spontaneous interest had been pruned into orthodoxy. The spiritual and intellectual outlook of man was firm—in fact it was rigid. Authority, not evidence, was the final arbiter; the term for disagreement was heresy. So powerful had the theologians become that even reflection upon the phenomena of nature invited attack and perhaps persecution. But such stagnation of the mind and spirit did not endure forever. Beginning in Italy, not in the great university of Bologna but in several places and cumulatively, there came in the Fourteenth and Fifteenth Centuries a revolt against the theologians and the scholastics. Now no one ever writes histories from the losers' point of view—especially when the losers have long been the authoritative element. And so it never becomes part of the tradition or the talents of those in authority to learn the earmarks by which to distinguish a powerful movement from mere sound and

fury, a dangerous maelstrom from concentric froth. And thus this growing movement in Italy flourished on the underestimation of the authorities.

Probably the growing leisure and wealth of the Italian city-states gave greatly increased margin for contemplation, for cultivation of the mind and of the spirit. Petrarch wanted Chrysolaras from Constantinople to teach Greek in Florence in 1396. Undoubtedly the fall of Constantinople fifty years later and the resultant deposed Byzantine scholars coming as emigrés to the West made available the enormous wealth of Greek and Roman classics and provided material for the eager young scholars to study and to imitate. In any event a tremendous force was set in motion. The Humanism of the Middle Ages was born—and man was reëstablished as the delightful object of fresh free contemplation, not the mere victim of theological orthodoxy and its allied political despotism. This kind of attention to man was fresh and free, even if one cannot claim that in the full sense it was new, since the classical authors had been similarly interested in human nature. The Italian humanists used the word *humanitas* to mean *culture* and happily quoted Protagoras the Sophist's "Homo Mensura" . . . "man is the measure of all things." I said that Humanism was born but if one recalls the literature of antiquity it is more appropriate to say that the humanist attitude was revived. Mankind has always been stirred more by resurrection than by birth, and Humanism was an enthralling resurrection. In it reverence for the residual wisdom of the ancients blended with astonished delight at the rediscovery here and now of human values. To use a current metaphor, a new yardstick was at hand—*homo mensura*. It was something like finding that your great-grandfather's watch keeps perfect time. The classical authors were found to be wise, witty, apposite, liberal, mellow, delectable—and all this in overwhelming contrast to the arbitrary dreariness of the theologians.

No wonder that such a delightful release of the spirit of man from exclusive theological preoccupations invited literary composition in the vernacular. The "here-and-now" received an intoxicating fillip from antiquity, from the classics which portrayed so graciously and so elegantly the enduring identity of human nature. Freedom comes so frequently from a recognition of limitations, and humanism through its mellow recognition of sameness in variety, produced and still produces fuller consciousness and freer faculties. What random heirlooms we

receive from the past! The degree of L.H.D. at Oxford crowns the curriculum of Litterae Humaniores. And Sir Walter Fletcher used to insist that our American usage of the word "Humanities" is historically unjustified since "the Humanities" comprised all those studies which were not "the Divinities." Therefore, he said, his favorite, Physiology, manifestly should rank as one of the humanities!

I trust this historical excursion does not deserve Lord Balfour's comment on a certain type of exposition of "what we understood much better before it was explained." Before proceeding further it may be well to reiterate that among the three eternal subjects of human speculation and curiosity—God, Man and Nature—Humanism has been an affirmation of the importance of Man and his values. Like other "isms," Humanism has presented its affirmations with some of the flavor of protest and revolt. And like other "isms," Humanism has been misrepresented by some of its adherents and misconstrued by many of its opponents.

The humanist is not a worshipper of the past. If he be retrospective it is to round out his perspective. His delighted and accurate familiarity with the Classics—whether Latin, Greek, Sanskrit or Chinese—is comparable to the satisfaction an experimental physiologist takes in the crucial and elegant experiments of Harvey or the wise nod of the clinician in reading the Hippocratic Oath. The humanist is not interested in the past merely because it is past. As the statistician likes a long series, not a short one, the humanist similarly likes the long accumulations from the past to illustrate the nature of man. No worshipper of the past, he is, however, far from being a modernist. Indeed the humanist would prefer to be taken for almost anything but a modernist. His particular aversion to modernism is perhaps due to his dislike of the pride that characterizes belief in all that is modern. In this point I side with the humanists. Indeed I would fain devote some effort to lay bare the nature and the full measure of our contemporary pride—so uniform and so unchallenged is it. Ours is the pride of the cheering section not of the lonely defiant individual. We are proud in a manner almost unknown to the past. The hubris of the Greek tragedy was typically the overweening pride of the individual: we scarcely comprehend the fascination for the ancients of this kind of tragedy, for our characteristic pride is of a different sort, we glory in an ineffable certainty that being modern, and all of us being modern together, we

are therefore insuperable. Our madness is not the pride of Goliath but of the Gadarene herd. In numbers, in numbers reassuring each other by deriding the past, we invite the disaster promised to the chief of the Seven Deadly Sins. To insist that the present is pregnant with perfection is a sort of provincialism not in space but in time. Indeed why say provincialism when there is still a better word—parochialism!

In contrast with the parochial satisfaction in all that is modern, the humanist insists upon the invariability of human nature despite changing creeds and customs. "*Plus ça change; plus ça reste.*" The humanist has this in common with the scientist—he is interested in those uniformities which repeat and reappear inescapably in the manifold of experience. The humanist interests himself in values which may advance without changing; the dogmatist, whether in science, religion, or politics, is too often concerned with things which change without advancing.

Though he who insists upon the sameness of human values may find the past and its classic literature peculiarly appropriate to his theme, the true humanist does not exploit the Classics. He does not feign authority, respectability or dignity by quoting Latin or Greek, or with careless inaccuracy appropriate from classical tradition. I wish I could say as much for the members of our own profession. Permit me one example of the spurious dignity and ignorant pretension the humanist disdains. The symbol of Aesculapius, the God of Healing, is a staff with one snake twisting around it. The symbol of Mercury, the God of Gaming, Commerce, and Communications, is the Caduceus, a staff with two snakes symmetrically entwined. The United States Public Health Service, the University of Chicago Press, the Medical Corps of the United States Army, innumerable hospitals and not a few medical societies hold doggedly to the decorative but rather misleading emblem of the patron of taking chances, taking profit and carrying tidings elsewhere. Granted that mercury is not without therapeutic indications, nonetheless architects and engravers, Trustees and Congressmen should be implored to confine the use of the Caduceus to the adornment of the Stock Exchanges, the Chambers of Commerce and Post Offices and be cured of seeing two snakes where one would better indicate the sober dignity of the Aesculapian tradition.

Now let us proceed to another confusion rather more subtle and more common. Humanism is not Humanitarianism. To confuse Humanism with Humanitarianism gives to the humanists a distress apparently

as acute and impassioned as we afford Socialists in confusing them with Communists. And perhaps rightly, for if words are the coinage of thought, no one will feel happy at being shortchanged. Both humanist and humanitarian reject a too exclusive preoccupation with God: the humanist because he is categorically opposed to too much of anything, the humanitarian because he feels the service of man to be the more cogent part of the First and Great Commandment. The humanitarian seems to substitute the service of man for the worship of God; the humanist wants balance and proportion between man's preoccupations with God and all man's other interests. The humanitarians would hold the humanists to be heartless intellectuals, contemplative and cultivated but not unselfish enough. The humanist, on the other hand, might find humanitarians offensive when they are over-zealous; Irving Babbitt's rapier flashes in this allusion to the humanitarians: "If it can be shown that there has been no vital omission in the passage from the Service of God to the service of man one may feel safe with all the altruists, from the third Earl of Shaftesbury to John Dewey."*

Again Humanism is not mysticism. It is in clear distinction from mysticism. Humanism appreciates rather than opposes religion. G. R. Elliott notes, "Theism at its worst fosters as nothing else can the proud imaginations of the human heart. Humanism, which in one of its most important functions is a criticism of religion, is essential for sound religious humility."** One wonders whether it is not essential for sound humility among scientists too. Humanism calmly declines to join in fanatic sorties of credulity or absolute surrenders of judgment. On the other hand the humanist is no advocate of immobility and repression. He is the partisan of give and take, of suppleness of adaptation, of easy sorties and sure returns, of the delicacy inherent in well-modulated strength, as R. B. Perry says, "of whatever influences conduce to freedom." It is quite natural that Osler, the humanist, took Aequanimitas as an object of his delighted attention.

Humanism possesses a quality curiously like the homeostasis of the organism; from any excursion too far out into the extremes of dogma or spiritual despotism it returns with persistent decorum to the nature of man as the center of operations and term of reference. The decorum of the organism is called homeostasis. Humanism stands for a similar

* Irving Babbitt, "Humanism—An Essay at Definition," *Humanism and America*, p. 35, edited by Norman Foerster, Farrar and Rinehart, New York, 1930.
** G. R. Elliott, "The Pride of Modernity," *ibid.*, p. 98.

decorum of the judgments and enthusiasms of the mind "*Homo mensura.*"

Let me quote from Irving Babbitt in Norman Foerster's "Humanism and America:"

> "As is well known, the word humanist was applied, first in the Italy of the Fifteenth Century and later in other European countries to the type of scholar who was not only proficient in Greek and Latin but who at the same time inclined to prefer the humanity of the great classical writers to what seemed to him the excess of divinity in the mediaevals. This contrast between humanity and divinity was often conceived very superficially. However, the best of the humanists were not content with opposing a somewhat external invitation of the Ciceronian or Virgillian elegance to the scholastic carelessness of form. They actually caught a glimpse of the fine proportionateness of the ancients at their best. They were thus encouraged to aim at a harmonious development of their faculties in this world rather than at another world felicity. Each faculty they held should be cultivated in due measure without one-sidedness or over-emphasis whether that of the ascetic or that of the specialist. 'Nothing too much' is indeed the central maxim of all genuine humanists ancient and modern.
>
> "In a world of ever-shifting circumstance, this maxim is not always of easy application. Whoever has succeeded in bridging the gap between the general precept and some particular emergency has to that extent achieved the fitting and the decorous. Decorum is simply the law of measure in its more concrete aspects. For every type of humanist decorum is in Milton's phrase, the 'grand masterpiece to observe.'"*

Does the role of the humanist begin to be clear? In the avoidance of extremes he warns and protects against the preoccupations of the theologian and of the specialist.

With the history and attributes of Humanism in mind we can now define more explicitly what valid relationship can obtain between Humanism and Science. I may as well say immediately that I think scientists are badly in need of Humanism. Bounden specialists that we are, if we are not to become lost in a fog of our atomized subdivisions of knowledge we must heed the humanist when he says to any one of us, "All

* *Op. Cit.*, p. 26.

that you say may be true but I must weigh its *value*, for I am a man and man has certain limitations and certain undetermined faculties, and long experience shows it is inane for him to be governed by frenzied conviction or fanatic obedience." It is scarcely a coincidence that the land of *fachmänner*—specialists—is become the land of frenzied conviction and fanatic obedience. As Humanism once provided the corrective to a too exclusive preoccupation with divinity, it will be wise ere long to look to Humanism for a corrective to man's too exclusive preoccupation with nature. The limitations of natural science are far more real than apparent, and far more important than we scientific moderns suppose. The limitations of a too exclusive preoccupation with science come down to this: Science offers neither meanings nor values. That is the defect of its quality. Nothing is to be gained by complaining that science offers man no system of values. It doesn't pretend to. We must look elsewhere for interpretations and meanings. Not even in the pronunciamentos of most psychologists are there as many abiding values for human beings as in great literature. And even if psychologists were to come upon what man needs, so pitiful is their ignorance of the art of expression that their findings would remain untranslated for a generation.

Just as the material of different sciences shapes the language and determines the type of thought proper to each science, so the permanent concern of the humanist with what conduces to man's freedom, to fuller consciousness, and a more graceful balance in living, produces a special power, a sort of style of mind and spirit. In such a style the connoisseur and the amateur join hands: a style appropriate to understanding and enjoying all of being human, not just to the elucidation of some part or function of being merely alive. The humanist, using the accumulated experience of human beings in their variegated business of being human, prepares himself to answer that devastating question, "What of it?" And in preparing us to reply to that question the humanist virtually says, "In your capacity as a human being you cannot afford to ignore the residual wisdom of the best of human beings. You must learn what they knew of the limitations and the freedoms appropriate to man." We hear a great deal nowadays among psychiatrists of the "total situation," "the total personality," "the cultural matrix," "the life situation." These crude groping phrases, these homeless neologisms seem like the outcries of a disoriented specialist in search of a set of values, values not merely for the America of 1940, but criteria for the art of being a human being

at any time. The most painful limitation of psychologists is their provincialism in time. Their field has been tilled in their manner not a hundred years, but apparently they will not bother with what was true before they came. More than most scientists, because they set out to study the psyche, they need to correct the absurdities and excesses of their specialism with the perspective of the humanist.

Let me repeat, Science offers us no system of values, no canons of good taste. Science is interested in what has logic, order, system and often in what has use. The humanist on the other hand, though not indifferent to logic, system, and order or usefulness, predominantly interests himself in what has value—in what long experience has shown to be the delights and satisfactions proper to mankind. There is a charming word—perhaps it is scientific slang to justify the right we have to our predilections, to our hobbies, to our enthusiasms be they never so irrational. The word is *ich-gerecht*. No humanist but would instantly wink with understanding at *ich-gerecht*—and waive all defensive explanations.

Humanism concerns itself with what has value, not what has use. Hans Zinsser, whose brilliant vitality illumined even the shadow of his death, expressed a restless dissatisfaction with the limitation of Science. Writing of course, of himself, he says:

> . . . He became, however, a profound admirer of Whitehead, who, it seemed to him, combined—in the wide horizon of his mature wisdom—deep erudition of the sciences with sensitiveness to aesthetic values, appearing in this regard to possess some of the qualities, less creative but perhaps more contemporaneously sound, of a Goethe. It was in Whitehead's diagnosis of the sick world that R.S. recognized his own, less learnedly arrived at, to the effect that, with the rapid development of industrialism and urbanization (both consequences of the scientific control of natural forces) there was a neglect of the "aesthetic qualities of the new material environment;" there was a limitation of the "moral outlook" at a time when it was most needed. The "moral pace of progress," says Whitehead, "requires a greater force of direction," but a grooved professionalism (also a consequence of the headlong rush of science) has brought it about that "the leading intellects lack balance" and "the task of coördination is left to those who lack either the force or the character to succeed in some definite career." The corrective, therefore, it seemed to R.S., should lie not in the checking of science, but

rather in catching up with it.

Thus, with Whitehead's assistance, R.S. thought he understood the general diagnosis. But that is as far as he got before he died. He stood before the problem as he often stood at the bedside of a dangerously sick patient, helplessly hoping for greater physicians to point a way of cure. He looked to art, literature, and criticism as the instruments through which this might come. For it seemed to him that what had happened was that mankind had been so busy planting the potatoes and corn and turnips of life that it had forgotten to tend the gardens. And now it had no gardens in the enjoyment of which it could find the reasons for which it had planted the potatoes and the turnips. For the arts and the spiritual values which they represent (and this was the pathology of the disease) had come to be regarded as trivial and not worthy of the efforts of serious men, a speculative commodity like stocks or postage stamps for rich collectors or a plaything for amateurs and eccentric incompetents; at best, a civilized amusement or a hobby.*

Where the humanist of the Fifteenth Century felt his natural interests restricted by the confines of theological dogma, the humanist of the Twentieth Century finds his interests and his aesthetic needs neglected by science. But the position of the Twentieth Century scientist is worse still. Can he derive a sense of meaning and significant direction from the one-sidedness of specialism? He may have a modernist's pride in the few trees he knows and their modern growth but what is to give him a sense of the forest, of the extent, the meaning or the beauty of the forest? Without some canons of taste and standards of loyalty to hold and cultivate in common with others, the true scientist feels—as some have confessed to me—a disquieting suspicion that his life taken as a whole is lacking in significance. There is something missing. Ah, there comes in the idea of value! Our scientific, modern, objective, practical view fails to note the age-old nature of man which if it is modern is also ancient—age-old but timeless. Would we moderns not find in Humanism and the humanistic attitude the most stimulating as well as the most congenial climate in which to develop our systems of values and meanings—most stimulating because of the length, breadth and catholicity of the humanistic tradition reaching as it does into remote antiquity, and most congenial because free from dogmatism and

* *As I Remember Him* by Hans Zinsser, Little, Brown and Company, 1940, pp. 422-423.

mysticism—both of which, when recognized, are unwelcome to the scientist's mind.

And if the scientist needs Humanism for himself, how much more is to be said of the scientifically trained physician upon whose store of faith, equanimity and sense of proportion and of value still others expect to depend? In the Gifford Lecture of 1914 Balfour* remarks that science "like common sense regards the things which are experienced as being themselves unaffected by experience." Let us grant that is true for most of the clinician's observation of death, of suffering, of disability or dysfunction! To witness death is not to affect it, to observe a disability is not to modify it. But the physician's task is not merely to observe; he must reason to a conclusion and proceed to treat. How long does the patient whom the physician is experiencing at the bedside remain "unaffected by the experience?" For a miraculous moment comes when the doctor becomes the treatment. And it is just there that science like a relay runner must pass the torch to Humanism. Science, the fruit of man's preoccupation with nature, must then give place to Humanism, the flower of man's experience with man. It is then that the riches of Humanism are needed, its wealth of corrective equanimity, its reflective philosophy of values, its insistence that the tastes of man may be of supreme importance to making his life worth living, and his death worth staving off.

Disease has many facets. Pain, disability, and death make up the most obvious among them. Over these three, pain, disability, and death, Science has won and will win yet more immeasurable victories. Let no doubt insinuate itself that the day of Science in medicine draws to a close. Quite the contrary—the application of biology, of physics and chemistry to disease is in the ascendant. But disease has other aspects—uncertainty, for example, or fear and shame and the distress at letting down one's fellow men. Indeed it is these human aspects of disease which are the hardest to bear, for which we physicians are most poorly prepared and in which scientific medicine has least to offer.

These are disturbances of a different order. They are not derangements within that neatly fitting boundary known as the human skin. More nearly they are disturbances within far wider boundaries, the patient's human relationships, his social protoplasm in which he feels himself, as it were, the nucleus, at once essential and dependent. We

* *Theism and Humanism*, The Gifford Lectures in 1914, p. 156, George H. Doran Company.

take it for widely known that disease distorts relationships of organs, tissues and functions within the body but only imaginative experience can convey an idea of the extent to which illness disturbs the relationship of the sick man to his personal matrix—to his family, his friends, his colleagues, and not least to his image of himself in this matrix, an arcanum, a secret inner chamber of his being, ineffably precious and delicate. Think, for example, of the domestic tyrant stricken with heart disease. He is totally unprepared for his sudden dependency upon his wife—of all people his wife whose married name had been Alice to tremble at his frown. And now she smiles at his helpless tantrums. It is not his shortness of breath, it is his tumble from omnipotence which infuriates and exhausts him. He cannot endure ceasing to dominate his colleagues, he cannot bear being pitied by his friends, ignored by his family.

Illness deranges us subjectively. It disturbs the values we have grown since infancy to attach to our status among other human beings. Can such derangements of our system of values be adjusted by science only, which admits it has naught to do with values and confines itself to experiences which are not modified by being experienced? The hasty answer would be certainly not. But that is wrong. Digitalis and rest in bed may reëstablish the domestic tyrant in full possession of his faculties and prerogatives. But if science fails him—ah, then it would be wise to have a physician who is a humanist—like Linsly Williams. For such a physician knows how people are and how to handle them without mechanical recourse to specialism or the narrow logic of any one system of study. The restless imaginative curiosity, the marvellously accurate observations, the stern and flawless reasoning of the scientist are glorious. His humility in the face of his conclusions is ennobling, but he is always in danger of error. His is a special frailty. The commonest error of the scientist is to assume that he is master of all the variables in his equation. One more factor than he is aware of may be his undoing. And when the practitioner of medicine is only such a scientist, that elusive additional factor may be himself—his own unnoticed effect upon the patient.

The true physician cannot remain outside the manifold of the events he observes, and upon this simple fact one may rest the whole argument for the alliance of Medicine with Humanism.

For if we admit that the physician as a *person* enters into the relation of doctor-to-patient, it is uncomfortable to see how meagre is the

cultural baggage, how callow the manners, how unexercised the imaginations and sympathies of our medical students must remain unless we open to them the resources of Humanism for the enrichment of their training. If in the years devoted to medical and premedical education he has omitted all cultivation of tastes and all reflection upon ultimate values and the selection of canons of human behavior, how can the young physician possess a culture richer than the random residues of his youthful background? How can we expect such a one to have the spiritual valences that will enable him to combine effectively with patients in the bewilderment and loneliness and anxieties of illness? Hans Zinsser told me in 1923 that he was looking for an assistant. "Only two qualifications are necessary—he must have read Tristram Shandy and be able to play the viola. I can teach him all the bacteriology he'll need to know!" If these were ever necessary for a bacteriologist what range of literature and artistic skill would be appropriate in a man fit to deal with persons as well as streptococci?

To the almost unlimited resources the humanists have made available in literature and the other arts a certain sort of physician remains conscientiously indifferent in the conviction that these records of the human spirit offer nothing of proper concern to the comprehension of man. I suppose that if the temptation to enjoy humanity through the humanities is not strong there need be no inordinate lament, but it seems sad that even timid pleasures are foresworn in the name of duty to patients. And the more so because some patients would rather be understood than be X-rayed, and rightly so.

Perhaps it is only because they are naturally imaginative, penetrating, quick in sympathies and broad in tolerance that some persons enjoy the great literature of Humanism. In that case humanistic tastes can be counted as the password by which we can recognize the radiant spirits in our profession. Or perhaps familiarity with litterae humaniores really nurses an infant sympathy and encourages a native tolerance so that imagination, sympathy and tolerance can be cultivated as well as merely recognized. In that event the study of great literature and the fine arts could serve as an invaluable supplement to medical science in the exercise as well as the preparation for the practice of medicine.

Before we leave the minor key of lamentation let us register regret that physicians repeat at times the paradoxical error of some scientists—the utterance of dogmatic finalities, in the presence, one might add, of

persons disposed to believe too readily. Such men behave as though today's science were definitive and final, yet all the while they devote their energies to its correction and modification. Science on the whole treats the manifold of experience as a causal series. The humanist treats it as a sequence of perceptions. The humanist then should supplement, not substitute, for the scientist, since the scientist runs the risk of failing to observe what he cannot explain in terms of cause and effect and the risk too of being dogmatic in his neglect of factors which do not lend themselves to his operations and form of study.

But on the whole physicians over the course of history give cause for robust rejoicing to the friends of Humanism. Until the Nineteenth Century they were not indentured in long service to the masters of natural science. Leonicenus, Rabelais, Linacre, Champier, and Dolet and Canappe were physicians intimately effective in spreading the New Learning and put Mediaeval Humanism enough in debt to Medicine to justify future borrowings in the opposite direction. Fracastorius, who wrote the first description of syphilis, was a professor of philosophy who practiced medicine and wrote poetry. As August Krey observes,* "Pagolo, friend of Cosimo di Medici, professor of astrology and other forms of mathematics, practiced medicine for a few friends." Vesalius, Agricola, Paracelsus, Conrad Gesner—the list is brilliant and long. So brilliant that this new learning largely centering at Pavia, Padua and Pisa, the universities favored by Milan, Venice and Florence respectively, began to overshadow Bologna, Oxford and Paris, whose only hope was to join the humanistic movement. Close as was the association with the classics in the earlier years, the knowledge of Greek and Latin is not the essence of Humanism, though it was the earliest vehicle for that New Learning. Hippocrates and Galen, the scholarly tradition of the Renaissance, the nomenclature of anatomy, physiology, pathology and therapeutics, have at least anchored us physicians to the classical tongues. From time to time we may drag anchor a bit as, when an elderly gynecologist had the classical warning *Primum non nocere* painted upon the wall of the operating theatre, with a translation by a modern colleague which ran instead of "Above all do no harm"—Primum non nocere—"The first time doesn't make any difference." Dean Briggs of Harvard is said to have remarked that although the A.B.

* *The Meaning of the Humanities:* Essay of August Krey on *History of the Humanities,* p. 68 (Princeton University Press).

degree no longer assured a familiarity with Greek and Latin, the degree of B.S. was a guarantee of their ignorance.

The essence, purpose and effect of Humanism in the Fourteenth and Fifteenth Centuries was to liberate the spirit of man from the despotism of theological and political orthodoxy by focussing attention upon man as the measure and frame of reference for all things. Humanism in any century has freed the faculties, widened the consciousness, reaffirmed the dignity and refreshed the gusty honesty of being human through clear-eyed acceptance of man's limitations and a happy insistence upon his potentialities.

It did more. With abounding grace, Humanism taught men to write again in the vernacular—a lesson sadly needed by medical writers of today. If we learned no more from the humanists than how to write English the linkage of Humanism and Science would be a godsend. With a public eager to understand more of science, the newspapers, despairing of the usual capacities of scientists to match the clearness of their understanding with the clarity of their expression, have begun to create a most valuable set of men called science writers. Since in democracies the support of research depends upon popular understanding of the nature of scientific work, scientists owe a great debt to these science writers. They have a delight in the use of clear, simple language and a realization of the potentialities of the here-and-now that reminds one of the mediaeval humanists, and like the humanists they have a feeling for the meaning and value of what they describe.

Meanwhile good writing in our professional journals is pitifully rare. Discriminating use of adverbs and adjectives is no mere literary embellishment. It is essential to the accurate and unambiguous recording of precise or complicated relationships. Where the order of events has meaning, excellence in narrative is no mere trick. James' *Chapter on Habit* and Osler's *Textbook of Medicine* are professional literature, it is true, but they transcend the usual boundaries of technical writing by virtue of their style. And who will deny Osler's freely acknowledged debt to the classical tradition of Humanism?

Somewhat as the science of statistics has developed a language to deal with series or classes of events in distinction to single events, so Humanism has developed a style of writing appropriate to express proportion and balance so necessary to the scientist who wishes to express his orderly comprehension, his power to put together again the frag-

ments he has obtained by analysis. Clear, vivid, enduring records of thought and feeling, of observation and inference come from a mind not too much enslaved to analysis or to seeing all phenomena in terms of causation. Even the act of observation may be disturbed by too much causal reasoning or too much familiarity with authoritative dicta. Wood Jones told me that for some twenty years the premedical students at the University of Adelaide had dissected the frog with the use of Huxley's manual. Now Huxley's manual was written for the dissection of *Rana temporaria,* the English frog. But the students were actually dissecting a frog anatomically different, *Rana australiensis.* In all that time only a scant dozen students had noted the differences between the frog they dissected and the frog in the textbook, and among the élite of those who noted that the frog was not just like the textbook not one student but concluded that his frog was *wrong.*

I trust this excursion into the need for better writing by scientists and perhaps especially by medical scientists will not seem unjustifiably remote from our consideration of the offerings of Humanism. For it is in his traditional economy and elegance of expression as well as his insistence upon balance and proportion that the humanist can serve as an ally if not a paragon. The scientist's lens to observe is bright: let not his mirror to reveal go unpolished!

I draw to a close. The limitation of science is that (quite honestly) it does not furnish us with tastes, significances, values, and meanings, though it provides us with an ever increasing diversity of what is interesting and useful. The attention of the humanist has for five hundred years and more been fixed upon tastes, values and meanings—the limitations and the freedoms of being human. Therefore, as may already be suspected, Humanism offers much to Science, especially in medicine where on occasion the physician will find a still imperfect science sadly inadequate to his patient's need. For in illness, fear, anxiety, shame, and uncertainty call for understanding, sympathy and imagination, courage and companionship, all among the Golden Treasury of Humanism. In the cultivation of these we must not rely merely on fortuitous circumstance. We physicians should resort to the treasure houses of literature and the arts, to the humanist and his familiarity with those values which are permanent for man.

As Humanism in the Fifteenth Century freed man from an extreme preoccupation with the exultations and the threats of the theologians,

it could serve now in the Twentieth Century to counterbalance the exultations and the threats of the specialists—whether they be mathematicians, physicists, biologists or psychologists. No, Humanism will still protest against exclusive preoccupations, against the limited horizon of dogma and finality. And therefore it deserves attention because it encourages independence, originality, honesty and a graceful proportionateness in understanding man.

I should feel gratified if during this hour you have been at times reminded of Linsly Williams. For in the best tradition of the humanist he had alertness to mankind, vitality of feeling, and a natural decorum. As a physician he had a clear-eyed but sympathetic recognition of the limitations of his patients and his friends and yet he knew how to encourage their potentialities and help them realize their hopes. He was a cultivated gentleman whose intellectual and esthetic tastes and beautifully balanced sympathies reached over a wide and delightful range. Far beyond most men he was a humanist capable of combining effectively with many kinds of persons to their advantage and delight, and to the welfare of us all.

TREATMENT OF BACTERIAL MENINGITIS*

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Any logical treatment of bacterial meningitis must be approached from two fundamental angles, chemotherapeutic and immunological. Evidence for the importance of the role of inhibition by chemotherapy is entirely convincing. The part played by immune bodies, either passively induced by serum treatment, or following spontaneous production as a result of the active infection, has in general been overlooked due to the natural supplanting of older methods by new and simpler ones. During the period of rapid progress in chemotherapy there has been a corresponding advance in methods of antibody production due to the chemical approach, and accurate quantitative analysis of the amount present in a given serum, thus putting this type of therapy on a firmer quantitative basis.

In an effort to gain an objective approach we must first refer to experimental evidence on the status of these two mechanisms. Here individual varieties of meningitis must be considered separately, but before doing so it will simplify the discussion to list those under consideration: Haemophilus influenzae, pneumococcus and meningococcus. They will be discussed together as an immunological group for they possess a similar pattern of chemical components acting as antigens, inducing chemical reactions in the body. Without going into details, this similarity may be described by stating that each of the organisms of this immunological group is surrounded by a capsule containing a specific carbohydrate, and in the course of metabolism this specific substance is excreted into the surrounding medium. This point deserves emphasis here for it is on this evidence that a single general plan of treatment combining drug and antibody is advocated for all three forms of meningitis.

Since the pneumococcus has been the most thoroughly studied of this group, the experimental evidence will be drawn mostly from this

* Read October 17, 1940, in the Graduate Fortnight of The New York Academy of Medicine. From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University, New York.

field. It has been shown that the capsular substance is the important element of the organisms, upon which their specificity and power to invade the human body depend. It is therefore logical that an effective therapy must be able to influence this mechanism. Since these organisms excrete this substance into any surrounding substrate in which they are multiplying, it is understood that the free carbohydrate must first be neutralized before the same substance in the capsule of the organisms can be attacked. The amount of free specific carbohydrate present in spinal fluid and blood of patients with pneumococcus meningitis is an index to the severity of the infection. It is also an index to the amount of anti-carbohydrate antibody necessary for its neutralization and recovery from such an infection. When the infection is of average severity and the biology of the organisms is interfered with and growth inhibited by chemotherapy, the natural antibody response takes care of this situation. It has been shown that in pneumonia the rise in anti-carbohydrate antibody in the blood correlates with crisis, whether it is spontaneous or induced. In drug treated patients and animals there is no evidence that antibody production is influenced in any way. There is a correlation between recovery and antibody production just as in the spontaneous process. The types of pneumonia which respond best to drug therapy also have the best antibody response. Free antibody produced by the infection can be detected earlier in the course of the disease when the patient is treated with drug than during spontaneous recovery, because there is production of less antigen or specific carbohydrate which it must neutralize. It would seem then that in recovery from pneumococcus infections, whether spontaneously, as the result of drug therapy, serum therapy, or a combination of these, antibody response is an essential part of the picture.

This work has demonstrated how the amount of antibody essential for recovery may differ with the severity of the disease and why a quantitative approach is necessary. You are all familiar with the great advance in immunological chemistry represented by an exact chemical method of quantitative analysis of the antibody in serum, whereby the amount of immune substance may be accurately determined and expressed in milligrams of immune nitrogen per cc. Analysis by this method parallels analysis by mouse protection methods indicating that it is the anti-carbohydrate antibody which is the protective one. This chemical determination eliminates the inaccuracies of the mouse protec-

tion tests. After a given original dose, the adequacy may be tested by objective means, either by the Francis skin test, or by testing the patient's serum directly for presence of free anti-carbohydrate antibody. It is only under such a regime that serum therapy can be evaluated either alone or in combination with drugs.

The other outstanding advance in this branch of immunology which has clinical application is production of therapeutic rabbit sera and the demonstration of their superiority over horse sera.

All evidence indicates that the biology of H. influenzae and meningococcus is similar to that of the pneumococcus. The parallelism is so great that there is every reason to assume that the role of the specific substance in the capsule is identical with that in the pneumococcus in influencing the severity of infection and in the formation of antibody spontaneously in patients and in production of antisera for passive immunization. The direct evidence on this point, while limited, indicates that the anti-carbohydrate antibody is the protective antibody in both anti-meningococcus and anti-H. influenzae serum. The quantitative analysis methods originally developed for anti-pneumococcus rabbit serum have been applied with success to H. influenzae rabbit serum by Michael Heidelberger. The methods used originally by Squibb's for purifying and concentrating the globulin fraction of anti-pneumococcus rabbit serum have likewise been applicable to H. influenzae antisera. Evidence suggests that free antibody in the serum of patients treated with H. influenzae antiserum is a valuable index to the adequacy of antibody for an individual instance. Rough quantitative tests on the amount of specific capsular substance free in the spinal fluid of meningococcus meningitis patients are of definite prognostic value.

First, I should like to discuss the treatment of meningitis due to H. influenzae, for it is in this field that we have derived most of our clinical and laboratory experience which is responsible for the formulation of a general plan of therapy applicable to the other two varieties belonging to this immunological group, that is, pneumococcus and meningococcus. The spontaneous mortality of H. influenzae meningitis varies from 90 to 100 per cent, depending upon the age distribution of the group analyzed. In patients less than 2 years of age the mortality approaches 100 per cent. Our own experience, prior to the use of the treatment to be described, showed no recoveries in thirty-eight patients, twenty of whom had been treated with horse serum and complement.

While the results of horse serum separately and in combination with drug therapy have altered the mortality significantly, the per cent of recoveries is still small. The best results reported in small groups showed a mortality of 67 per cent while large groups show a less favorable prognosis under the same therapy.

There have been a number of reports of single recoveries under drug therapy alone. One paper collected the results of eighteen cases treated with sulfapyridine alone with five recoveries, a mortality of 72 per cent. Only three of the recovered patients were under 6 years of age. In eighty-two patients treated by sulfanilamide, there was a mortality of 88 per cent. In thirty of these, serum was used in addition and four of these recovered. While experience shows there is more inaccurate bacteriology on this organism than any other, it is clear that recoveries do occur when drugs alone, both sulfanilamide and sulfapyridine, are used. This evidence supported by the demonstration of inhibition of this organism by all three drugs in common use, both in vitro and in vivo, warrants the use of drug therapy for its inhibiting effect. The selection of the best drug is difficult at the present time on the basis of objective evidence. Our own very limited results with all three drugs in mouse protection tests fail to show any significant difference. Verbal reports from one institution indicate superiority of sulfathiazole and from another that results of mouse protection tests with all the drugs were so discouraging that that form of therapy has been discontinued in influenza meningitis. Their clinical results at that time were in the same direction. Our own clinical experience fails to show a difference between sulfanilamide and sulfapyridine (sulfathiazole has been used in two patients, only one of whom recovered). Until the question of permeability of the meninges for sulfathiazole has been more thoroughly investigated, this drug should not be used in meningitis.

According to current views, antibody would seem to be an essential part of the recovery mechanism, whether it be manufactured by the patient as the result of the infection in the presence of drug therapy or whether antibody is introduced by serum therapy. In the present state of our knowledge derived from clinical experience and the advances in immunology, one must conclude that a combination of antibody and drug therapy should yield the best results in this disease.

Experience with the method to be described is still too limited to

be evaluated with accuracy. However, the results of its use in several institutions have been so encouraging that a detailed description seems warranted.

We have attempted to apply the fundamental principles discussed under recovery from pneumococcus infections to the therapy of influenza meningitis. The foundation which made possible the transfer of these principles was laid by Pittman. While there is no direct evidence on this point all evidence indicates that the ability of this organism to invade is linked closely to the production of free specific carbohydrate.

Our interest first centered around the production of rabbit serum in 1937, since our experience with horse serum alone had been very discouraging. All the knowledge of the biology and chemical structure of the pneumococcus has been utilized in the production of rabbit anti-influenza antibody. Heidelberger's quantitative chemical analysis of the amount of antibody produced under various circumstances with different types of vaccine has enabled us to increase the antibody tenfold over early lots and to put the dosage on a quantitative basis. The dosage of the first patients treated prior to the above work was based on volume of the serum tested by only relative methods, as was all serum therapy in the past. Sulfanilamide was the most thoroughly understood drug at the time and this was combined with the rather weak serum used on a volume basis. Since the first three consecutive patients treated by this method recovered and since subsequent experience showed the total amount of serum used on the first three to contain less than 100 milligrams of antibody nitrogen per patient, this amount of antibody in concentrated form has been considered as probably a sufficient total dose for the average case.

On the assumption that a given quantity of antibody would be more effective if utilized mainly against the carbohydrate in the capsule of the organism, an attempt was made to speed up the urinary excretion of the free carbohydrate present in the body by intravenous fluids containing sulfanilamide prior to the administration of serum. In this way inhibition of the organisms by chemotherapy should prevent the liberation of large amounts of free carbohydrate into the blood and spinal fluid. This method of control of the amount of specific carbohydrate present is important in the cases of average severity of a duration of 2 to 3 days or longer, and in the fulminating types in which no drug therapy has been used. The body under these circumstances theoretically con-

tains large quantities of free specific carbohydrate. In addition to the most efficient use of a given amount of antibody this speeding up excretion of free specific carbohydrate should prevent the violent reactions of the very severe forms of meningitis when a large quantity of antibody is given at one time. It has been assumed that such reactions are probably the result of the sudden uniting of large quantities of antigen and antibody. Death was frequently the result.

Since the prognosis in any form of therapy depends upon the duration of the disease prior to its administration, a brief description of the most rapid effective means of accurate diagnosis of H. influenzae will be given. When Gram-negative rods or even when pleomorphic diplococci, suggesting morphology of pneumococcus or meningococcus, are seen on direct smear, the possibility of H. influenzae should be entertained. When confusion does arise, it is due to poor Gram stains and lack of familiarity with the great variation in form of this organism. The presence of this organism may be definitely established within a few minutes when type specific rabbit diagnostic antisera are used for detecting capsular swelling of the organisms. The procedure is identical with that used for typing pneumococcus by the Neufeld method. Unless capsular swelling of the organisms is produced by type b diagnostic serum, there is no rationale for using any of the sera available, for they are active only against this type. Fortunately, almost all cases of influenzal meningitis in children are due to type b. Diagnostic typing sera are available commercially from E. R. Squibb & Sons. If no organisms are present on direct smear, 1 cc. of the purulent spinal fluid is planted in 10 cc. of Levinthal broth in a small flask. The size of surface in contact with the air is important. This is the ideal method for detecting very small numbers of H. influenzae. Until a definite etiology is established, sulfanilamide is given alone. When the H. influenzae is shown to be type b the following treatment is carried out: As soon as a continuous intravenous drip is set up, 0.1 gram per kilogram of sulfanilamide is given by infusion. After this, 0.1 gram per kilogram is given through a continuous intravenous drip over a 4-hour period in 40 cc. of Ringer's or saline, per kilogram. Following a 3-hour period of forced fluids, provided sensitivity tests are negative, rabbit antiserum in an amount containing 25 milligrams of antibody nitrogen is given intrathecally. Additional antibody is then added to the continuous drip for intravenous administration—50 milligrams of antibody nitrogen for a case of average

severity and 75 milligrams for severe forms of the disease. The concentrated antibody is diluted in 200 to 300 cc. Ringer's or saline containing sulfanilamide. The speed of the drip is arranged so that the diluted antibody is administered over a 2-hour period. The estimated total amount of antibody needed is given in one dose on the theory that it will be utilized more efficiently and recovery will be more rapid. The adequacy of this original dose is checked 1 hour later by testing the patient's serum for its ability to produce capsular swelling of the organism. Lumbar punctures are performed daily. If, 24 hours later, the spinal fluid smear shows no organisms, if the chlorides and sugar are rising and the protein and cell count are falling, and if free antibody persists in the patient's serum in such a concentration that a 1:10 dilution produces capsular swelling, no further serum is indicated. The organisms in the suspension used for this purpose must contain good capsules. The original spinal fluid serves as an ideal suspension for this purpose if organisms are numerous and if 0.4 per cent formalin is added within an hour of withdrawal. Tubes of the spinal fluid, after the addition of 0.4 per cent formalin, are placed on ice promptly and kept there except for 5 minutes daily when they are taken out to remove a small specimen for use; under these circumstances the encapsulated organisms remain in good condition. If it is necessary to use a culture for this suspension, the importance of a young culture in Levinthal broth (4 to 6 hours incubation) must be stressed. The capsules start to degenerate after this period. In any case, one should check the condition of the capsules by known diagnostic sera before using them for detection of free antibody in the patient's serum. The administration of the drug is continued by intravenous drip or by subcutaneous route for the first 24 hours, maintaining a concentration of 10 milligrams per 100 cc. of blood. Oral route is then used, if the patient's coöperation permits. This can be accomplished by giving 0.1 gram per kilogram for the 20 hours following the first 4-hours' treatment outlined above. The dose given during the first 24 hours totals 0.3 gm. per kilogram. The subsequent administration of 0.1 gram per kilogram per day, divided into six doses at 4-hour intervals, is continued for one week after the first sterile spinal fluid is obtained. Sulfanilamide is recommended because in our experience sulfapyridine depresses the white blood cells in the young age group more frequently than any other drug. The evidence indicates that unless the neutropenia is influenced by discontinuing the drug and

using daily transfusions and pentnucleotide, the prognosis is extremely grave. This suggests that phagocytosis is an essential part of the defense mechanism.

While this method has been advised and used for the majority of patients, it is hoped that a more extended use of the intravenous route alone for serum therapy will prove to be the ideal method. Four patients have been treated by this method and all have recovered. Limitation of serum therapy to this route is permissible at present in institutions where the staff is equipped to examine the patient's serum at intervals for free antibody, and the laboratory facilities permit accurate daily quantitative chemical analysis of the spinal fluid. When significant increase in the spinal fluid sugar and chlorides and decrease in protein is seen 24 hours after intravenous serum, this constitutes the earliest and most delicate index of the patient's improvement and no further serum is indicated if these criteria continue in the direction of recovery and if free antibody can be detected daily in a 1:10 dilution of the patient's serum. Without this evidence one must rely on the presence or absence of organisms in stained smears of spinal fluid—obviously a very gross test. Clinical improvement in the early stages is frequently very misleading as prognostic evidence. Most patients show a temperature response to the serum which is quite prolonged at times. However, when no intrathecal treatment is used, other than drainage, the clinical response is more rapid and reliable. The value of spinal fluid cultures, if negative, in determining subsequent therapy depends upon the methods used for culture. When the spinal fluid is planted as described previously, a negative culture after 24 hours' incubation is good evidence of improvement.

If serum therapy is confined to the intravenous route, a minimum of 100 milligrams of immune nitrogen should be used initially. Evidence of free antibody in a 1:10 dilution of the patient's serum one hour later indicates that this dose has been sufficient for the time being. If such evidence is lacking another 50 milligrams of immune nitrogen diluted in 150 cc. of saline is given through the continuous drip over an hour period.

Twenty-eight patients have been treated with the rabbit serum described. Two of these were moribund and died in a few hours. Of the twenty-six who lived 40 hours or more, seventeen recovered completely, resulting in a mortality of 35 per cent.

TABLE I

Recovered Group—Serum and Sulfanilamide

Name	Age	Previous Duration of Illness	Drug Used	Antibody			Blood Culture	Time to Sterilize Spinal Fluid
				I.V. cc.	I.T. cc.	Mgm. Total		
G.M.	19 mo.	4 days	1 week	155	67	<100	0	72 hours
M.W.	3 yr.	24 hours	11 days	180	38	<100	0	48 hours
W.W.	15 mo.	2-6 days	1 week	140	85	<100	+	24 hours
W.S.	5 yr.	2 days	2 weeks	0	15	<10	0	24 hours
R.D.	2 yr.	24 hours	23 days	20	20	180	+	24 hours
A.C.	19 mo.	5 days—P	1 week	15	5	100	0	24 hours
F.J.	2 yr.	48 hours	8 days	15	5	100	+	24 hours
J.F.	23 mo.	48 hours	19 days	29	10	195	+	6 days
C.H.B.*								
J.G.*								
V.P.*								

* Complete recovery of these patients treated at other institutions has been reported but details of course have not yet been received.

First, I should like to present the significant details of the eleven patients who recovered following treatment with serum and sulfanilamide (Table I). The first four patients were treated with unconcentrated serum which explains the large volume of serum used. The other seven were treated with concentrated antibody solution produced and analyzed chemically by E. R. Squibb's according to the methods which we have worked out with Heidelberger. This product is now available commercially. In five patients, the total estimated dose was given at one time with rapid and complete clearing of the meningitis. In one, small doses were given at 24-hour intervals through an error in calculation and the process was more prolonged, requiring 6 days for complete sterilization.

Table II shows the group who recovered following treatment with sulfapyridine and serum and also the group treated with serum alone or a small amount of combinations of drugs. The two patients who were treated with sulfapyridine and serum are of interest in demonstrating the inhibitory action of this drug alone for periods of 10 days or over. The clinical condition of these two patients was remarkably good considering the duration of the meningitis, so that the demonstration of organisms with ease on direct stained smears was a great surprise.

TABLE II

Name	Age	Previous Duration of Illness	Drug Used	Antibody			Blood Culture	Time to Sterilize Spinal Fluid
				I.V. cc.	I.T. cc.	Mgm. Total		
Recovered Group—Serum and Sulfapyridine								
E.A.	14 mo.	2½ weeks S and P	P alone 3 days and then 18 days	285	90	200	+	72 hours
A.Z.	5 yr.	10 days	P 2 weeks	200	0	100	0	48 hours
Miscellaneous Group with Serum Therapy								
K.P.	4 yr.	48 hours	No drug	26	0	125	+	36 hours
M.B.*	5 yr.	34 hours 10 cc. 0.5% pron 30 gr. T	S & T 48 hours	200	0	120	0	24 hours
R.G.	3 yr.	4 days P and stopped	P 4 days and S 6 days	30	0	135	0	24 hours
E.M.*	2½ yr.	24 hours	S 2 days, P 2 doses T 8 days	25	5	150	+	24 hours

S—Sulfanilamide, P—Sulfapyridine, T—Sulfathiazole.
* All drug discontinued because of leukopenia.

The organisms were well encapsulated. The first patient was treated with sulfapyridine alone in large doses parenterally for three days in Babies Hospital without influencing the picture. Both recovered promptly on addition of serum therapy. The miscellaneous group is of great interest in that the first three had only intravenous therapy. In two of these, antibody was demonstrated in the spinal fluid. The first had no drug therapy, the second had drugs for 48 hours only and the third had no drug for a 24-hour period after the first two days, following which sulfathiazole was given in such doses that only minute amounts could be detected in the spinal fluid. Three of these patients were treated with Squibb's concentrated antibody.

Table III lists the same data for the eleven fatal cases. These have been divided into three groups. In five, serum therapy has been guided by presence of free antibody in the patient's serum (sulfapyridine has been used with serum in four of the five). In three of these the spinal fluid has become sterile, the chemistry has improved and the temperature became significantly lower when a neutropenia developed following which an exacerbation occurred with a rapid downhill course.

TABLE III
FATAL GROUP

Name	Age	Previous Duration of Illness	Drug Used	Antibody I.V. cc.	Antibody I.T. cc.	Antibody Mgm. Total	Blood Culture	Time to Sterilize Spinal Fluid	Leukopenia	Remarks
Five Adequately Treated Cases										
W.G.	7 yr.	3 days	P 7 days	340	130	235	+, —, +	3 days, then + 7th day neg.	0	Otitis media
F.	3 mo.	3 days ?	P 2 days, T 16 days	28	25	175	+, —, +	72 hours for 6 days, then +	0	Otitis media
J.S.*	2¾ yr.	8 days P	P 12 days large dose	200	66	133	0, +	24 hours, neg. 16 days	+	Healed & fresh meningitis at P.M.
D.S.*	7 mo.	3 days	P large dose	390	98	300	+, —, +	24 hours, neg. 3 days	+	
M.W.*	3 mo.	3 days ?	S 4 days	45	15	180	+, —, +	48 hours, + after 24 hours	+	
Treated Without Application of Present Criteria										
S.N.*	3 yr.	?	P	30	49 H.S.†	127	0	48 hours, neg. 9 days	+	Died 1 month
J.W.	2¾ yr.	4 days	S 2 days	115	56	50	+	Not sterilized	0	Died in 44 hr.
B.H.	1½ yr.	5 days	S 2 days		46	15	+	Not sterilized	0	Died in 40 hr.
J.T.	2½ yr.	5 days	S 4 weeks	200	100	90	+	Not sterilized	0	Sinus thrombosis
Death Too Soon for Evaluation of Therapy										
B.M.	5 mo.	?	S 12 hours	40	20	160	+	Not sterilized Scant growth	0	Died in 12 hr. hemorrhagic necrosis of brain
J.M.	3½ yr.	4 days	No drug	20	0	100	+	?	0	Died in 6 hours.

S—Sulfanilamide, P—Sulfapyridine, T—Sulfathiazole.
† Horse serum.
* Spinal fluid had become sterile and sugar approached normal until onset of leukopenia.

One of these patients became completely well by all criteria for a period of sixteen days. The mild leukopenia present during drug therapy continued after the drug was stopped and thrombocytopenic purpura developed, following which a fulminating form of influenza meningitis appeared and death occurred in 24 hours. At autopsy there was a healed meningitis and a fresh one. The last two patients did not live long enough to evaluate the therapy. Since both were treated with a large quantity of antibody intravenously without proper dilution and prior to treatment with drug or fluids, the question arises whether death was hastened by the treatment received. There were four other patients treated without application of the method recommended. One was apparently recovering until leukopenia developed. Two died within 48 hours of admission and were inadequately treated from a quantitative standpoint. The remaining patient who was not treated according to present standards showed lateral sinus thrombosis on autopsy.

Pneumococcus Meningitis

The rapid development of new chemotherapeutic agents against pneumococcus infections certainly confuses the picture for the practitioner during the experimental phases. Three drugs have already had laboratory and clinical trial against pneumococcus infection, sulfanilamide, sulfapyridine and sulfathiazole. All have some inhibitory action in vitro and in vivo. Sulfapyridine and sulfathiazole are definitely superior to sulfanilamide but these two are not significantly different in their influence on this infection in mice. All clinical work, thus far, indicates the same degree of effectiveness in pneumonia in man when similar blood concentrations are obtained. Since evidence, thus far, points to the fact that it is very difficult to obtain adequate spinal fluid concentration of sulfathiazole, sulfapyridine is the drug of choice in pneumococcus meningitis.

From a survey of the literature of the limited experience with the use of sulfapyridine alone in the treatment of the pneumococcus meningitis, it is already clear that the prognosis in adults has been improved significantly. However, the mortality in infants under two years of age has not been affected. It is generally agreed that antibody administration is an essential part of therapy in the latter age group. In older children and adults, until greater experience improves the present mortality figures of approximately 50 per cent under drug

treatment alone, I believe serum should be combined with chemotherapy. All the theoretical evidence which I have outlined indicates that the latter treatment should materially improve the prognosis. Experimental work indicates that the combination of serum and drug in mice is more effective than the sum of the two separate effects would lead one to expect, and suggests a synergistic effect. This is logical since the inhibitory mechanism of the drug should enable smaller quantities of the antibody to be effective. The clinical experience with this type of treatment, combined drug and antibody, is still limited. This fact is definite, however. On the whole when the patient does recover under drug therapy alone, the course of the disease is more prolonged and there is greater tendency to exacerbations than when serum and drug are used in combination.

The method of combined treatment with type-specific rabbit serum and sulfapyridine which we recommend is essentially the same as that used in H. influenzae meningitis. One-tenth gram (0.1 gram) of sodium sulfapyridine per kilogram in 15 cc. per kilogram of saline or Ringer's is introduced intravenously as soon as the meningitis is recognized to be pneumococcus which should be within a 20 minute period after the fluid reaches the laboratory in the great majority of cases. For, except in the rare extremely early case, the organisms are easy to find on direct stained smear, their morphology is quite characteristic and typing may be performed by the Neufeld method directly from the spinal fluid. During the next 4-hour period one aims to introduce intravenously 40 cc. of fluid per kilogram body weight. One per cent sodium sulfapyridine in a quantity sufficient to give 0.1 gram per kilogram of the drug forms a varying portion of this volume depending upon the weight of the patient and the remainder is made up by saline or Ringer's solution. Here, too, it is hoped that the free specific carbohydrate will be excreted during this period by the forcing of fluids. The serum is administered in diluted form over a 2-hour period just as described for H. influenzae meningitis. In a patient with infection of average severity it is advisable to start with 100,000 units or 100 milligrams of immune nitrogen of rabbit type-specific anti-pneumococcus serum. The adequacy of such a dose may be detected by the method described previously, which tests for the presence of free anti-carbohydrate antibody in the patient's serum by the Neufeld reaction. If free antibody cannot be demonstrated, additional antibody is indicated immediately. In

obviously severe infections, until more evidence is obtained on this point, 200,000 units are indicated. Our experience with influenza meningitis and the knowledge of the specificity of sulfapyridine for pneumococcus leads us to try the intravenous route alone for serum treatment for the first 24 to 36 hours, unless the spinal fluid shows a decrease in sugar and increase in cell count. Under such circumstances spinal drainage is performed at 8-hour intervals for this period, hoping that changes in pressure relationships may increase permeability of the meninges for the antibody from the blood. Daily examination of the patient's serum for free antibody and the chemistry and cultures of the spinal fluid guide one in further serum therapy just as in influenza meningitis. Intravenous drug is continued for at least the first 24 hours. After administration of 0.2 gram per kilogram of the drug during the first 4 hours, a dose of 0.1 gram per kilogram is used during the remaining 20 hours. Following this, the oral route is used if condition of the patient permits and 0.1 gram per kilogram is used for each 24-hour period through one week after the spinal fluid has become normal. If the meningeal reaction is poor so that the first spinal fluid specimen on direct smear has the appearance of a culture of pneumococci with few pus cells, one intrathecal dose of 50,000 units is given in addition to the intravenous serum. If the criteria previously described for determining an excess of antibody are present 24 hours later, no further serum is given by any route.

Meningococcus Meningitis

The comparison of the efficacy of drug and serum alone in meningococcus meningitis is very difficult at the present time. The sporadic form of the disease varies so greatly in virulence that only an epidemic would serve as a proper background for evaluation of the efficiency of each one of these forms of therapy. Under such circumstances alternate case selection on a large scale would answer the question. However, so far as present evidence goes, there is general agreement that sulfanilamide alone is equal to or superior to serum therapy. In mice, meningococci are susceptible to both drugs when used alone but sulfapyridine is effective in lower concentration than sulfanilamide.

It has just been during the last five years that an attempt has been made to put serum therapy on a quantitative basis. The agglutinin titer method for analyzing the strength of a given serum has been shown to

be very inadequate. With the production of a rabbit antiserum of high anti-carbohydrate antibody content analyzed by chemical methods and used in the manner described for the other two forms of meningitis, the mortality figures previously reported for serum therapy should be improved.

Unless an epidemic occurs there is every reason to expect the majority of patients to respond to sulfanilamide alone. For this reason, at the present time it seems advisable to start all patients on sulfanilamide first by a large infusion containing 0.1 gram per kilogram. After this, 0.1 gram per kilogram is given through continuous intravenous drip over a 4-hour period in about 40 cc. per kilogram of Ringer's or saline solution. The administration of the drug is continued by intravenous drip or by subcutaneous route through the first 24 hours by giving 0.1 gram per kilogram for the remaining 20 hours. The subsequent administration of 0.1 gram per kilogram per day, divided into 6 doses at 4-hour intervals, is continued for one week after the first sterile spinal fluid is obtained. The diffusion of the drug into the meninges is so efficient that intrathecal treatment is unnecessary. However, daily lumbar punctures are recommended in order to follow the spinal fluid cell count and chemistry in order to be guided by more objective evidence than the patient's clinical condition. Experimentally drug-resistant strains are encountered frequently. If the criteria, discussed previously, fail to demonstrate marked evidence of improvement 48 hours after start of chemotherapy, serum in a diluted form should be given over a 2 to 3-hour period by a continuous intravenous drip. Estimation of the total amount of antibody necessary is difficult to assess, for experience with the use of serum has been gained when a purely volume basis was used. Mouse protection tests now used by the National Institute of Health permit the use of units. In severe forms 100,000 units should be used. The examination for evidence of free antibody in the patient's serum may be applied following the serum administration to determine whether a sufficient dose has been given. In the present state of our knowledge serum is not indicated by intrathecal route, unless objective signs of improvement fail to occur 24 hours later.

If the patient represents the fulminating type, serum therapy seems indicated after a 4-hour period of drug therapy and forcing of fluids.

The qualitative precipitin test on the cleared spinal fluid served as a valuable prognostic aid in a group of serum treated patients during

TABLE IV

THE RESULTS WITH VARIETY OF DRUG COMBINATIONS AND SERUM. ANALYSIS OF 26 PATIENTS TREATED WITH RABBIT SERUM

	Recovered	Fatal	Total
Treated with Sulfanilamide	11	4	15
Treated with Sulfapyridine	2	4	6
No drug	1		1
Sulfanilamide and Sulfathiazole—48 hours	1		1
Sulfanilamide and Sulfapyridine	1		1
Sulfanilamide—2 days, Sulfathiazole—8 days	1		1
Sulfathiazole		1	1
Total	17 or 65%	9 or 35%	26

an outbreak in Baltimore in 1936. Perhaps this may be of value in selecting the patients on whom serum therapy is indicated in addition to drug therapy.

The results of combined treatment in humans is too limited to warrant comparison with groups treated by drug alone. In addition, until quite recently, the national standards of potency, based on agglutination tests, prevented a quantitative approach to this type of treatment. There is general agreement that both antitoxin and antibacterial serum aid in decreasing toxicity. Mouse experimentation shows very consistent results with this type of treatment. When either sulfanilamide or sulfapyridine is combined with serum therapy, the protection is greater than the effects of the sum of the two.

SUMMARY

It has been shown that in the present state of our knowledge a combination of antibody and chemotherapy offers the best prognosis in both H. influenzae and pneumococcus meningitis. In meningococcus meningitis the marked susceptibility of the organism in sporadic cases to both sulfanilamide and sulfapyridine warrants a trial period with drug alone. However, in fulminating types of the disease and severe forms in infants intravenous serum is indicated after a 4-hour period of drug administration.

THE NEWER KNOWLEDGE OF VITAMIN K*

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One of the most dramatic and stimulating series of events of recent years concerns the discovery of Vitamin K, its isolation and the synthesis of various active compounds, the recognition of its role in the body and its clinical application in the study and treatment of deficiencies. Extensive work has been done largely in the past five or six years, and we can only touch on some of the major developments in this presentation.

Dam[1] in 1934 first postulated that the hemorrhagic disease which he and others had observed over the previous five years in chicks on a variety of purified low-fat diets was due to a deficiency of a specific antihemorrhagic factor in the diet and a year later proposed the designation of this factor as Vitamin K (Koagulations Vitamin).[2] This hemorrhagic tendency noted incidentally was at first attributed to scurvy, but subsequent work[3, 4, 5, 6] indicated that this was not the case, nor was it due to lack of, or cured by any of the other then recognized accessory dietary factors.

The fact that the diets which produced the hemorrhagic tendency were of low-fat content suggested the fat-soluble nature of the vitamin, and this was subsequently proved[2, 7, 8, 9] when it was obtained from natural sources by extraction with fat solvents. It is found most richly distributed among the green, leafy plants and vegetables such as alfalfa, spinach, cabbage, cauliflower, kale, carrot-tops, and seaweed, and to a lesser extent in others. In general, it may be said to be most abundant in the chlorophyll-containing structures and is therefore to be found in higher concentrations in leaves than in seeds, fruit or roots. Another rich source is putrified fish meal.

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Investigation of the hemorrhagic disease of chicks due to K avitaminosis indicated that this was associated with a prolonged clotting time[6, 10] and it was suggested[11] that this was due to hypothrombinemia. Dam, Schønheyder and Tage-Hansen[12] and Quick[13] produced definite proof of this, the latter by tracing the progressive fall in the level of the plasma prothrombin in chicks on K-deficient diet which in turn was corrected by feeding the vitamin. Vitamin K deficiency of severe grade is very difficult to produce in mammals by dietary means alone in the absence of disturbances of its absorption or metabolism, although the more moderate grades can be produced on carefully extracted diets. In 1937 Greaves and Schmidt,[14] who had previously shown that the absorption of the other fat-soluble Vitamins A and D was interfered with when bile was absent from the intestinal tract, were able to produce hypoprothrombinemia in rats with common duct obstruction or biliary fistula. Quick, Stanley-Brown and Bancroft[15] in 1935 drew attention to the prolongation of the clotting time by their prothrombin test and suggested that the defect was primarily a diminution of this component of the clotting mechanism. Later Warner, Brinkhous and Smith[16, 17] and others demonstrated this defect in jaundiced patients.

Since Vitamin K deficiency is synonymous with diminished prothrombin activity of the plasma, considerable importance attaches to methods for the estimation of this component of the clotting mechanism now in current use. In speaking of the plasma prothrombin we should realize that the chemical nature of this substance is unknown, although it is closely bound to the globulin fraction of the plasma. These tests merely assay the activity of the prothrombin, and thus, perhaps, indirectly indicate the amount present.

The first of these devised by Quick[18] is performed as follows: Mix the contents of one capsule of thromboplastin with 5 cc. physiological saline solution containing 0.1 cc. (10/M) sodium oxalate. Incubate this at approximately 45° C. (113° F.) for 10 minutes, then centrifuge at slow speed for 10 minutes. Draw off the resultant extract with a pipette and place in a test tube or bottle. This solution of thromboplastin is stable for periods of time up to two hours. Draw 4.5 cc. blood from a large vein with a large needle. Add the blood to 0.5 cc. of sodium oxalate (10/M) in a centrifuge tube, mix and centrifuge at low speed for 5 to 10 minutes. Add 0.1 cc. clear plasma to 0.1 cc. thromboplastin in a small test tube and mix. Add rapidly 0.1 cc. calcium chloride (40/M). Hold

test tube in bath at 37.5° C. while tilting very gently every second or two and note the length of time in seconds elapsing before the formation of a definite clot. Normal blood shows a clotting time of 15 seconds or less. If the clotting time exceeds 18 seconds, precautionary measures should be recommended. This method has the advantage of ease of performance and is sufficiently accurate for most clinical observations.

Warner, Brinkhous and Smith[19] in 1935 brought out a method which is more cumbersome and requires considerable experience for its most accurate performance, but which in the hands of many workers, including those in our own laboratory, gives more accurate and consistent results and is more desirable for research purposes. This test is performed as follows: Blood to be tested for prothrombin is oxalated with 1.5 per cent sodium oxalate in the proportion of 0.5 cc. sodium oxalate to 4.5 cc. of blood (1:10). It is centrifuged and 1 cc. plasma to be tested is removed. To this sample 0.1 cc. fresh thrombin is added to clot out the fibrinogen present. The thrombin is made by adding to 0.15 cc. oxalated plasma 0.3 cc. normal saline, 0.15 cc. thromboplastin and 0.15 cc. calcium mixture, and winding out the clot which forms in about 20 seconds. An excess of thrombin remains after the clot is removed and this is used immediately, as it disappears rapidly. After standing 15 minutes while the fibrinogen clots out, the fibrin clot is removed, leaving free prothrombin. Of this prothrombin, 0.1 cc. is diluted with oxalated saline. The dilution is then added to a mixture made up of equal quantities of normal saline, calcium and thromboplastin and incubated in a water bath at 28° C. for 30, 45, 90 and 120 seconds, timing from addition of dilution. After incubation, 0.1 cc. of fibrinogen is added and the clotting time measured with a stop watch. The dilution for the sample tested is that one which will clot in 15 seconds when incubated for 30 or 45 seconds for dog plasma and 90 or 120 seconds for human plasma. Incubations other than the one clotting in 15 seconds must clot in time longer than 15 seconds. A normal sample is compared with other samples tested and the results are expressed in per cent of that normal.

The same authors[20] have more recently published a much simplified method which can be performed at the bedside or in the office and which gives results quite satisfactory for clinical purposes. The technique is as follows: Place 0.1 cc. thromboplastin in a small serologic test tube. The tube is then filled to a 1.0 cc. mark with freshly drawn blood from the patient. The tube is inverted once over the finger to secure com-

plete mixing and then tilted gently every second or two. The time is noted in seconds for the formation of a clot. Normal blood usually clots in 25 to 30 seconds. However, it is advisable to run a standard on normal human blood as a check. Then the percentage of normal is given as follows:

$$\text{Prothrombin Activity in per cent of normal} = \frac{\text{Clotting time of normal blood} \times 100}{\text{Clotting time of patient's blood}}$$

A more recent test has been brought out by Allen and his associates[21] but as yet we have had no clinical experience with it.

The most accurate is the dilution method of Warner, Brinkhous and Smith, but, as it is more intricate and time-consuming, it may not find wide clinical application, as either the method of Quick or the simplified method of Warner, Brinkhous and Smith is sufficiently accurate for clinical use. In all our own work except for a few of the earlier clinical cases investigated, the dilution method was employed and in our own laboratory has an error of plus or minus 3 per cent.

The discovery of the existence of Vitamin K and of its sources led to the production of more and more concentrated extracts until Dam and his co-workers[22] in 1939 reported a concentrate which assayed 20 million Dam units per gram. Similar extracts were obtained by McKee[23] and by Binkley and his associates.[24, 25] It was then recognized that while both were very active, the Vitamin K_1 obtained from alfalfa was distinctly different from that from fish meal, which came to be called K_2. Work then began in earnest on the elucidation of the structure, and K_1 has been shown to be 2-methyl-3 phytyl-1, 4-naphthoquinone. The structure of K_2 has not yet been worked out. Almquist and Klose[26] reported that phthiocol, a substance which had previously been isolated from the tubercle bacillus, possessed Vitamin K activity. This, now called K_3, has a structure similar to K_1 but has an hydroxyl instead of a phytyl group attached to the third carbon atom.

In July 1939, four groups of workers[27, 28, 29, 30] independentely reported that another compound, 2-methyl-1, 4-naphthoquinone, possessed Vitamin K activity. This synthetic substance now known as K_4 is generally accepted as having the highest activity of all those so far studied, and seems indeed to be even more potent than the crystalline vitamin compounds obtained from natural sources by extraction.

It is soluble in oil but only slightly soluble in water. It can be given by mouth in either solvent as well as intramuscularly. For intravenous

use a more soluble salt is usually employed. When given by mouth, bile salts are also administered but these are of course not necessary when it is injected parenterally. Our own preference is for the injection in oil by the intramuscular route as it is free from toxic symptoms and the effect of a single dose is maintained for a considerable period—as long as eleven days in one of our cases. Intravenous injection is also well tolerated and may act slightly more rapidly, but does not seem to be quite as prolonged in its effect.

It should be emphasized that the numerical designation of the various compounds with Vitamin K activity does not indicate, as in the members of the B complex, any qualitative differences in their action. So far as is now known they differ only quantitatively.

After absorption from the intestine the vitamin is stored in the body tissues, and, no evidence has yet been presented for any endogenous origin aside from the intestinal tract. The vitamin is present in appreciable quantities in the feces of even deficient animals, its production being attributed to bacterial action, but recent experiments with isolated intestinal loops in our laboratory cast some doubt on this, as the vitamin is still present in definite amounts after the loops have become sterile. To date, however, the factor of excretion has not been entirely ruled out. Once Vitamin K is absorbed, it is intimately concerned with the production of prothrombin, and while widely distributed throughout the body, the level of the plasma prothrombin in dogs with normal livers has been shown[31] to be a straight line function of the concentration of the vitamin in this organ.

While formerly it was thought that prothrombin was formed in the bone marrow and distributed to the blood from the platelets, this point of view has been discredited since these elements cannot be shown to yield prothrombin, and because neither the thrombopenia produced experimentally by irradiation of the bone marrow[32] nor that encountered clinically in thrombopenic purpura is associated with any decrease of the plasma prothrombin. On the other hand, a mass of evidence has accumulated to indicate that the liver is the chief and perhaps the only site of formation of this substance. Thus, damage to the liver by chloroform[33] or by partial extirpation[34] is accompanied by a marked fall in the plasma prothrombin, and even such minor injury as gentle massage for 25 minutes[35] causes a decrease of as much as 25 per cent. As recovery occurs, the level of the plasma prothrombin returns to normal.

Total hepatectomy, studied independently by ourselves[36] and by Warren and Rhoads,[37] is followed by a drop in the plasma prothrombin level to below 10 per cent in 14 hours, and we have been able to show that in the absence of the liver even massive doses of Vitamin K fail to prevent this fall in any way. Thus, it is clear that for the normal effect of Vitamin K, it must not only be absorbed, but the liver must be normal for its optimum effect in maintaining the plasma prothrombin. In normal animals (dogs) the plasma prothrombin can be shown to disappear from the circulation during passage through the lungs[38] as in 85 per cent of our animals we were able to show an average difference of 10.6 per cent (extremes of 4 and 19 per cent) in the prothrombin levels of blood from the right and left heart. This is definitely not due to oxygenation of the blood and cannot be shown in afferent and efferent blood of any other organs.

Another important consideration is the fact that there is remarkably little difference in the plasma prothrombin levels of normal individuals, and that, even with relatively large doses of Vitamin K, it does not seem to be possible to elevate the plasma prothrombin activity as measured by these tests above the normal level. For this reason there seems to be little danger that overdosage of the vitamin will produce thrombosis. It should be stressed that Vitamin K therapy is consistently unavailing except in patients with conditions associated with diminished levels of the plasma prothrombin. It cannot be expected, therefore, to be of benefit in such diseases as hemophilia or thrombocytopenic purpura.

Let us consider, then, certain states associated with lowered levels of plasma prothrombin and the role of Vitamin K in their production and therapy. While because of their spectacular nature the severe grades of Vitamin K deficiency associated with actual hemorrhagic tendency have occupied the limelight, it is important to recognize the lesser degrees of deficiency as from them much of great importance can be learned.

As mentioned above, it is questionable whether K avitaminosis of severe grade ever occurs from purely dietary causes, perhaps because of the synthesis of the vitamin in the intestinal tract, but in association with severe nutritional conditions definite hypoprothrombinemia of moderate grade is frequently seen, which yields promptly to appropriate therapy. Similarly, intestinal drainage either through fistulae or through prolonged use of gastric or intestinal suction may prevent a sufficient absorption of the vitamin and thus may depress the level of the plasma prothrombin.

In addition, certain individuals have come under our observation in whom there seems to exist a latent or subclinical K avitaminosis in the presence of normal dietary intake which appears to be based on some defect of absorption even though bile is present in the intestinal tract. In such persons the prothrombin is usually about 60 per cent of the normal and fails to rise appreciably after the oral administration of 2-methyl-1, 4-naphthoquinone with or without bile salts. Further evidence that the defect is primarily in the absorptive mechanism is obtained by the parenteral injection of the vitamin which is promptly followed by a rise in the plasma prothrombin level to normal.

Other instances of K avitaminosis to be explained on the basis of inadequate intake or poor absorption are found in connection with the intractable diarrheas as in ulcerative colitis or in sprue. Here, contrary to the rule outlined above, the depression of prothrombin may be so severe as to fall below the critical bleeding level (about 20 per cent of normal) for the individual, and hemorrhage may ensue. Usually these cases, too, yield promptly to parenteral therapy, and the administration of the vitamin and bile salts by mouth may be helpful. We have seen several cases falling into this category and Thomas T. Mackie from the Colitis Clinic of Roosevelt Hospital reports that in 23 per cent of their cases the plasma prothrombin was definitely reduced.

The most striking type of K avitaminosis due to failure of absorption is seen in cases of obstructive jaundice. Here, due to absence of bile from the intestinal tract the fat-soluble Vitamin K is not absorbed and seriously depressed plasma prothrombin levels result. Because the body normally has a fairly large reserve of the vitamin, the fall is gradual and may not reach the hemorrhagic level for some time, but the reserve may have become depleted through insufficient intake or for other reasons so that the duration of jaundice cannot be taken as a possible indication of the plasma prothrombin level. When the prothrombin reaches the critical level for the individual, which varies somewhat but is usually about 20 per cent of normal, bleeding occurs. Such a case is illustrated in Figure 1 which depicts the course of a patient with common duct obstruction before Vitamin K therapy was available. Bleeding is particularly apt to occur after operation as Lord[35] has shown that manipulation of the liver such as may be required in operations on the common duct may themselves significantly lower the prothrombin content of the plasma. Thus, a patient whose preoperative prothrombin

was diminished but still above the critical level might bleed due to further depression following an operative procedure.

In the absence of liver damage, the response to therapy is dramatic as illustrated by the patient's course as it appears in Figure 2.

Numerous clinicians have noted that patients with varying degrees of liver damage may fail to respond adequately or at all to the administration of substances with Vitamin K activity.[17, 18, 39, 40, 41, 42] In our own series a considerable number have failed to show a satisfactory response, and as will be discussed later, this finding can be used as an index of liver damage. A particularly striking clinical example of the role of the liver quite comparable to the hepatectomy experiments in animals is seen in Figure 3 which depicts the course of a 50-year old woman who was admitted to the hospital with a temperature of 40° C. She had had symptoms of gall bladder disease for 18 years and had been somewhat jaundiced for 5 weeks. On admission her condition was so critical that she was treated conservatively with clyses, blood transfusions and Vitamin K and bile salts for a period of 4 days and was then subjected to cholecystostomy. At operation an inflammatory mass was found around the lower portion of the gall bladder overlying the common duct. The administration of Vitamin K (Klotogen) was quite effective at first, and by one week after admission the plasma prothrombin was 100 per cent of normal. Despite continued vitamin therapy and blood transfusions, however, it suddenly fell thereafter and remained at a low level. The patient subsequently died, and at postmortem examination thromboses of the hepatic artery and portal vein with massive necrosis of the liver were found. Microscopic examination of the thrombi indicated that they had been deposited at about the time that the precipitous fall in the plasma prothrombin occurred.

A similar but less severe example is seen in Figure 4, showing the course of the plasma prothrombin level in a patient with cirrhosis of the liver. The concentration of prothrombin here was 70 per cent before treatment with 2-methyl-1, 4-naphthoquinone, but it continued to fall even after relatively large doses until it reached 48 per cent.

Severe enterocolitis or sprue with intractable diarrhea may be associated with marked depression of the plasma prothrombin level due, probably, to deficient diet or diminished absorption, or both. In some of these cases the administration of Vitamin K and bile salts may be effective in overcoming the deficiency and parenteral therapy is often

strikingly so. Figure 5, however, represents the course of a patient with sprue treated orally before the preparations suitable for parenteral therapy were available. There was no response, and although the amounts used here—about 5,000 units per day—were small compared to our present day dosages, they had been effective in many other types of cases.

A number of investigations indicate the presence of low plasma prothrombin levels in new-born infants and of extreme hypoprothrombinemia in cases of hemorrhagic disease of the newborn.[43, 44, 45, 46, 47, 48] These authors, using methods other than the test of Quick, have found that the normal new-born infant has a plasma prothrombin level of from 20 to 30 per cent of that of the mother, and that in hemorrhagic cases the values are even lower. Quick and Grossman,[49] on the other hand, using Quick's method, failed to find such consistently low values in the newborn, but did find[50] a marked diminution from the first to the sixth day of life. It seems, therefore, that the prothrombin levels of normal infants are precariously near the hemorrhagic level and seem to bear a rough percentage relationship to that of the mother. In premature infants[47, 48] the prothrombin has been found to be less than 10 per cent of that of the mother. In all infants, however, the level gradually rises after the fifth or sixth day and reaches the adult normal value at about 10 or 11 months.

While hemorrhagic disease is associated with diminished prothrombin, there cannot be said to be any definite level at which bleeding occurs. Thus, some cases may have values as low as 10 to 15 per cent without hemorrhage, while in others bleeding is seen at a somewhat higher level.

Fortunately, however, the condition can be prevented by the administration of the vitamin to the mother before delivery, and may be spectacularly cured by means of oral or parenteral therapy in the infant. Figure 6 illustrates the course of such a patient from the Pediatrics Department of the New York Hospital who was treated with 2-methyl-1, 4-naphthoquinone.

Finally, what we believe will be one of the most fruitful fields of study of Vitamin K concerns its use in the investigation of liver function. As was suggested above, the response of a subject with a normal liver but lowered plasma prothrombin, to adequate administration of Vitamin K is so prompt and so striking that it is possible to use this

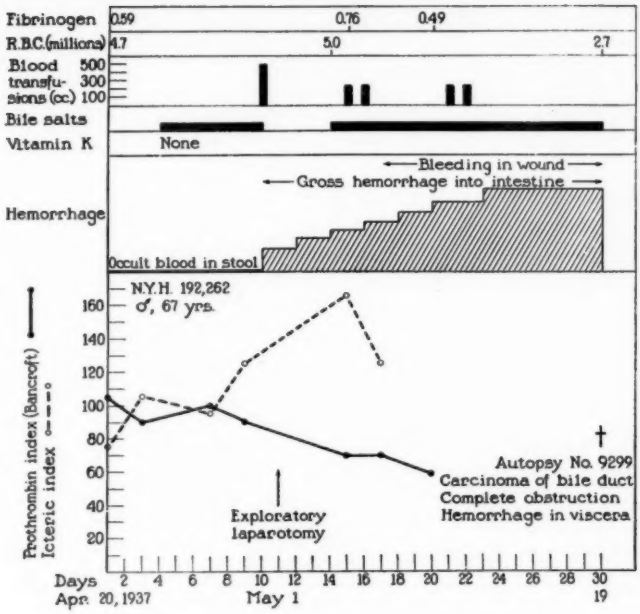

Figure 1

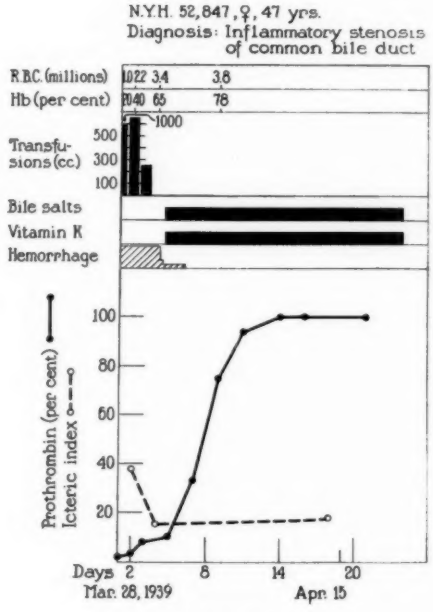

Figure 2

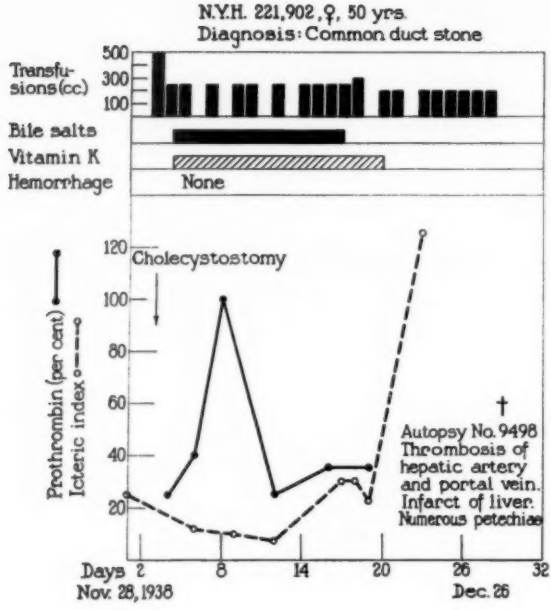

Figure 3

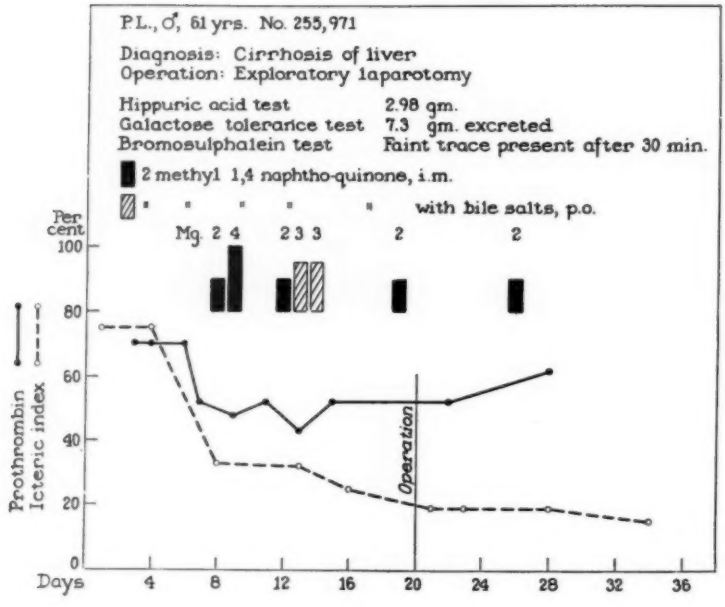

Figure 4

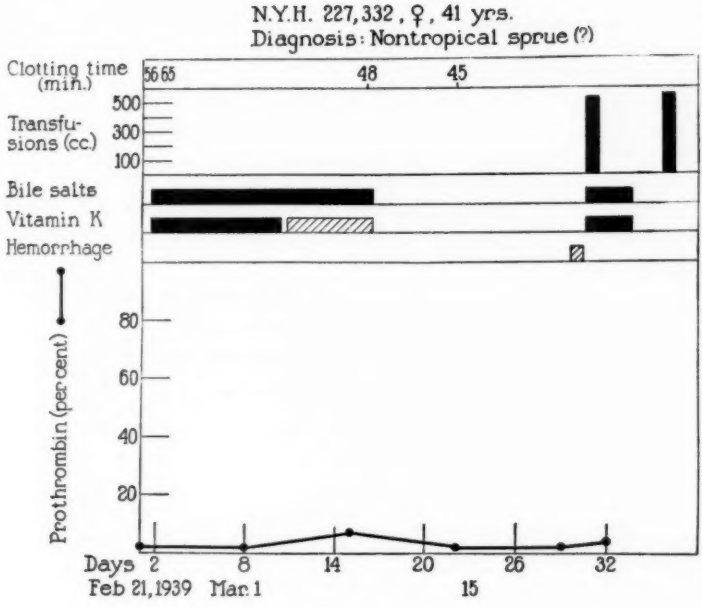

Figure 5

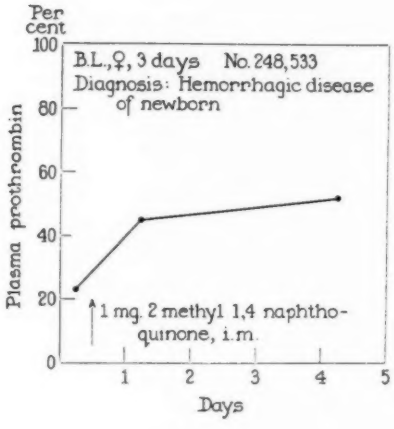

Figure 6

response as an indication of the state of the liver. Experience with this test in a considerable number of cases, including more than forty jaundiced patients, has led us to impose considerable confidence in it. Indeed, we have come to feel that it possesses certain advantages over even the best of the current tests of liver function in that—at least so far as the prothrombin-forming activity of the liver is concerned—we are enabled to distinguish between what we may call functional disturbances and those due to organic liver disease. It seems fair to say that within limits, the level of the plasma prothrombin, if previously depressed below 80 per cent, indicates the performance of the liver, while the response to Vitamin K—in our studies to the intramuscular injections of 2 mgm. of 2-methyl-1, 4-naphthoquinone—indicates whether the diminished prothrombin was due to functional disturbances, such as inadequate intake or absorption, or to organic disease. The test finds one of its greatest fields of usefulness in distinguishing between jaundice of extrahepatic origin—due, for example, to obstruction of the common duct by tumor or stone—and that due to parenchymal liver disease. In brief, we have found that in the former the plasma prothrombin either remains above 80 per cent, or, if it be depressed, rises following the intramuscular injection of 2 mgm. of 2-methyl-1, 4-naphthoquinone by more than 10 per cent in the first 48 to 72 hours. In intrahepatic jaundice the prothrombin, which here is uniformly depressed, either fails to rise by this amount or continues to fall. In forty jaundiced patients, twenty-five of whom were suffering from common duct obstruction of one sort or another and in fifteen of whom the icterus was due to catarrhal jaundice, cirrhosis, liver abscess, etc., the test was almost 100 per cent correct. The findings were checked by operation or postmortem examination in all cases of extrahepatic jaundice and in nine of those in whom it was of intrahepatic origin. The remaining six patients followed clinical courses typical of catarrhal jaundice.

Further applications of this test remain to be studied, but work now in progress suggests that its simplicity and accuracy may prove very useful in studying alterations in liver function in a wide variety of conditions.

TABLE I

EXTRAHEPATIC JAUNDICE—COMPARATIVE ACCURACY OF TESTS

Type of Test	*Authors*	*Total No. of Cases*	*Cases with Normal Response*	*Per Cent Correct*
I. Galactose Tolerance	Schiff & Senior	21	20	95%
	Banks, Sprague & Snell	68	41	60%
	White	12	11	92%
	Lord & Andrus	7	4	57%
II. Serum Phosphatase	Rothman, Meranze & Meranze	29	25	86%
	Cantarow & Nelson	31	21	68%
III. Hippuric Acid	Quick	3	2	67%
	Snell & Plunkett	12	2	17%
	Lord & Andrus	6	6	100%
IV. Flocculation	Hanger	25	25	100%
V. Response of Plasma Prothrombin to 2-Methyl-1, 4-Naphthoquinone	Lord & Andrus	25	25	100%

TABLE II

INTRAHEPATIC JAUNDICE—COMPARATIVE ACCURACY OF TESTS

Type of Test	*Authors*	*Total No. of Cases*	*Cases with Abnormal Response*	*Per Cent Correct*
I. Galactose Tolerance	Schiff & Senior	65	63	97%
	Banks, Sprague & Snell	31	17	55%
	White	34	25	74%
	Lord & Andrus	9	7	77%
II. Serum Phosphatase	Rothman, Meranze & Meranze	24	18	75%
	Cantarow & Nelson	22	12	55%
	Lord & Andrus	2	1	50%
III. Hippuric Acid	Quick	13	12	92%
	Snell & Plunkett	6	4	67%
	Lord & Andrus	6	4	67%
IV. Flocculation	Hanger	38	33	87%
V. Response of Plasma Prothrombin to 2-Methyl-1, 4-Naphthoquinone	Lord & Andrus	15	15	100%

TABLE III—JAUNDICE OF EXTRAHEPATIC ORIGIN

No.	*Case*	*Diagnosis*	*Duration of Jaundice*	*Icteric Index*	*Level of Plasma Prothrombin*				*Net Change*
					Initial	*After Injection*			
						24 Hr.	*48 Hr.*	*72 Hr.*	
1	J.B.	Common Duct Stone	2 days	62	57	61	—	65	+ 8*
2	R.A.	Ca. Head of Pancreas	3 wks.	50	68	—	77	72	+ 9*
				(2nd Adm.)	64	76	92	—	+28
3	H.H.	Common Duct Stone	2 wks.	16	70	80	—	—	+10
4	M.P.	Obstr. Jaundice due to Ca.	2 days	30	78	—	—	88	+10
						100% in 96 hours)			
5	J.M.	Ca. Head of Pancreas	2 wks.	150	75	85	—	—	+10
6	M.P.	Common Duct Stricture	off & on	75	61	72	—	73	+12**
7	E.B.	Cholelithiasis Cholecystitis	off & on	30	68	83	—	—	+15
8	P.D.	Ca. Head of Pancreas	2 wks.	150	52	52	—	70	+18
9	F.G.	Common Duct Stone	3 mos.	60	66	85	—	—	+19
10	R.M.	Cholangeitis, Subacute Cholecystitis & Pancreatitis	2 days	33	76	95	—	95	+19
11	L.G.	Cholecystitis	1 day	47	68	85	—	89	+21**
12	J.L.	Common Duct Stone	2 days	50	75	—	100	—	+25

* These patients were operated upon immediately after the initial prothrombin was run. The effect of the operative trauma influenced the rise.
** These patients received more than one dose of 2-methyl-l, 4-naphthoquinone.

TABLE III [Continued]—JAUNDICE OF EXTRAHEPATIC ORIGIN

No.	Case	Diagnosis	Duration of Jaundice	Icteric Index	Level of Plasma Prothrombin				Net Change
					Initial	After Injection			
						24 Hr.	48 Hr.	72 Hr.	
13	K.H.	Ca. Head of Pancreas	3 wks.	62	48	75	—	—	+27
14	L.M.	Acute Cholecystitis, Cholangeitis	4 days	—	52	80	—	80	+28
15	C.G.	Cholelithiasis Cholangeitis	2 wks.	26	52	75	80	—	+28
16	C.D.	Common Duct Stricture	3 yrs.	75	68	82	100	—	+32
17	R.S.	Ca. Head of Pancreas	1 mo.	125	52	71	71	90	+38**
18	S.F.	Ca. Head of Pancreas	6 mos.	31	61	71	100	—	+39**
19	B.O.	Acute Cholecystitis, Cholangeitis	1 wk.	28	60	—	—	100	+40
20	R.L.	Acute Cholesystitis	3 days	150	38	—	80	—	+42
21	M.G.	Common Duct Stone	1 mo.	150	47	78	—	95	+48
22	K.F.	Common Duct Stone	1 wk.	25	52	—	100	—	+48
23	F.S.	Common Duct Stricture	3 wks.	150	18	67	50	—	+49
24	P.P.	Cholelithiasis Cholecystitis	off & on	75	38	80	87	—	+49
25	D.O.	Common Duct Stricture	3 mos.	150	38	70	—	100	+62

* These patients were operated upon immediately after the initial prothrombin was run. The effect of the operative trauma influenced the rise.
** These patients received more than one dose of 2-methyl-1, 4-naphthoquinone.

TABLE IV—JAUNDICE OF INTRAHEPATIC ORIGIN

No.	*Case*	*Diagnosis*	*Duration of Jaundice*	*Icteric Index*	*Level of Plasma Prothrombin*				*Net Change*
					Initial	*After Injection*			
						24 Hr.	*48 Hr.*	*72 Hr.*	
1	A.G.	Cirrhosis with Hepatitis	9 days	300	48	14	—	14	—34
2	J.D.	Cirrhosis with Central Necrosis	2 days	—	52	48	—	33	—19
3	F.S.	Cirrhosis	———	12	35	—	—	25	—10
4	P.L.	Cirrhosis	2 wks.	75	52	43	—	52	— 9
5	E.J.	Hepatic Insufficiency	Unknown	60	41	—	36	—	— 5
6	E.T.	Catarrhal Jaundice	3 days	107	71	—	70	—	— 1
7	D.M.	Catarrhal Jaundice	3 wks.	71	66	68	65	—	— 1
8	L.E.	Catarrhal Jaundice	10 mos.	50	23	23	—	22	— 1
9	G.G.	Liver Abscess	4 days	75	52	—	—	52	0
10	M.S.	Catarrhal Jaundice	2 wks.	60	67	—	68	—	+ 1
11	M.K.	Cirrhosis	———	12	39	—	37	40	+ 1
12	T.H.	Multiple Liver Abscesses	———	14	48	52	—	52	+ 4
13	J.K.	Cirrhosis	8 days	46	32	—	—	38	+ 6
14	S.M.	Catarrhal Jaundice	3 wks.	100	70	—	—	76	+ 6
				225	76	76	—	—	0
					52	—	52	—	0
15	C.M.	Subacute Hepatitis	10 days	40	60	60	70	65	+10

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MASSIVE DOSE CHEMOTHERAPY BY THE INTRAVENOUS DRIP METHOD*

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INTRAVENOUS introduction of drugs, in the experimental animal, was first employed in 1665 by Robert Boyle,[1] the physicist, and Christopher Wren,[1] the architect, following the discovery by William Harvey[2] of the circulation of blood. A year later, Richard Lower[3] practiced direct transfusion of blood from one to another animal. In 1667, Denis[4] transfused sheep blood into man. The severe and fatal reactions, so readily understood today, resulted in legal condemnation of blood transfusion in humans.

Throughout the Eighteenth and Nineteenth centuries, blood transfusion remained in disuse though, in the Restoration Period, phlebotomy was liberally practiced, as the art and literature of those times amply attest.

Many of the technical problems relative to intravenous therapy were solved in the years that lapsed between the early experiments and the researches of the Twentieth century. The science of bacteriology was born. Asepsis was practiced in the preparation of solutions, materials, and the technical procedure. Venipuncture was simplified by the introduction of hollow steel needles, which replaced the ancient quills and cannulae.

The Development of Intravenous Infusion. In 1831, Latta[5] employed intravenous saline solution in the treatment of Asiatic cholera. During the succeeding half-century, saline infusions continued to be employed fitfully and irregularly. Reactions must have been severe and numerous, due to bacteriologic and chemical impurity. With the introduction of asepsis and improvement in chemical methods, these latter hazards were overcome and interest in intravenous infusion was stimulated.

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The Advantages of the Intravenous Route of Administration

In laboratory experiments as well as in clinical therapy, the intravenous route of administration is the most direct, effectual and practicable method for the introduction of soluble preparations into the circulating stream. Intraärterial and intracardiac[6, 7] injections are technically difficult, more apt to be dangerous and accompanied by hemorrhage. Their use should be reserved for special circumstances, such as recent and sudden cessation[8] of the circulation when resuscitation yet may be possible. Enteral, subcutaneous and intramuscular injections result in: (1) Delayed entrance of the vehicle into the circulating fluid through uncertain and irregular absorption; (2) local inflammation from the deposition of irritant material in connective tissue or muscle; (3) mechanical limitation of the bulk of the agent to be introduced parenterally, through painful and awkward clyses; (4) possible modification through digestive or oxidative phenomena, or even destruction of a potent agent prior to its entrance into the circulating stream; (5) difficulty in obtaining, maintaining or rapidly calculating the effectual concentration in the blood of the potent agent, except in rare instances, e.g., the derivatives of sulfanilamide.[9]

Disadvantages of Intravenous Therapy

Despite the advantages of intravenous therapy, several deterrents limited its usefulness. There was the purely technical difficulty of venipuncture and the local inflammatory changes incident thereto. Of more importance were the untoward sequelae, often dangerous and occasionally fatal, which occured during or immediately after intravenous injection. These are not attributable pharmacologically to the specific drug action of the injected substance. So great was the fear of these sequelae that Sollmann[10] wrote: "Intravenous injections should be avoided for they always imply a greater risk to the patient than do the other methods of administration" ***** "The danger is not so much in errors of the surgical technique, which is generally rather simple, but in the fact that the injection of a foreign substance into the blood stream alters the equilibrium of its colloids and thus may result in alarming and even fatal reactions" ***** "Almost all substances may apparently produce such reactions in some individuals under conditions that are not understood and cannot be foretold." (Hanzlik and Karsner,[11] Hanzlik, De Eds and Taintor.[12])

The untoward reactions following intravenous therapy have given rise to many investigations and much speculation. Pyrogenic substances[13, 14] have been isolated and described. Alterations in temperature or hydrogen-ion concentration[15] of the infusates have been held culpable. The mechanism of "colloidoclasis" has been postulated. The resemblance of the symptomatology to anaphylaxis gave origin to the concept of an "anaphylactoid" phenomenon.[16] A mechanical factor such as acute dilatation of the heart[17] has been suggested. Embolization[18] has been suspected. Syphilologists, employing the arsenicals, coined the phrase "nitritoid crises" as their contribution to the pathogenesis of these unpleasant toxic phenomena.

Reactions occurred irregularly and were unpredictable. Clinicians felt a sense of insecurity about intravenous medication. Particularly in desperate situations of clinical practice, where vigorous therapy was clearly indicated, intravenous medication was withheld or performed hesitantly through fear that untoward phenomena might snap the thin thread by which life was, at least for the time, suspended. The problem of the untoward sequelae associated with intravenous injection was clouded in mystery.

The Velocity Factor in Intravenous Therapy

In the United States, the pioneer in modern intravenous therapy was Rudolph Matas. Matas[19] gave the first intravenous infusion with physiological saline solution on July 12, 1888 at the Charity Hospital in New Orleans. In 1891, appeared his first publication, citing nineteen clinical experiences with *slow* intravenous infusion. The indications for therapy were shock, hemorrhage and exhaustion. The technique differed from current practice in that vessels were exposed, ligated and cannularized rather than entered by direct venipuncture. M. Friedman,[17] of Langersdreen, was probably the first continental exponent of intravenous infusion, though his earliest publication concerning "Dauerinfusion" did not appear until 1913, more than twenty years after the published record of Matas. Friedman was prompted to devise and adopt the drop method through an erroneous concept of acute dilatation of the heart. It is historically interesting to quote from a recent letter of Dr. Matas,[20] who writes: "If we extend the period of my experience with the intravenous method from June, 1888, when I administered the first infusion at the Charity Hospital, to the present moment (July, 1939) we realize

that a little over a half century has elapsed between these dates, during which the whole history of intravenous therapy, including remedial injections, infusions, "drip" and blood transfusions, has been evolved, developed and matured from its primitive, timid and rare beginnings to its present surpassing importance in contemporary medical practice."

"It is interesting to note as an illustration of the extraordinary pace of modern scientific achievement that this relatively new chapter in surgical history, in all its practical utility and vast therapeutic significance should have come into existence and fulfilled its most visionary realization within the span of a human life, in fact, well within the period of my own professional life and activities."

In 1923, after a lapse of thirty-two years, Matas[21] again reported on massive infusions of saline solution and, for the first time, used the term "intravenous drip." The continued intravenous drip by regular drop instillation into the veins (phleboclysis) first came into use on his services at the Tuoro Infirmary and later at the Charity Hospital in the fall of 1910. At first (1910-1911), Matas writes: "The intravenous drip was used timidly and tentatively for critical cases only, in which proctoclysis and hypodermoclysis could not be depended on for prompt and continued action." The transfer from the rectal to the intravenous drip was not made "until after long hesitation in fear of thrombophlebitis, embolism by air or clot, cardiac dilatation and pulmonary edema from venous depletion." Matas stressed the factor of velocity, recognizing that rapid injection was capable of producing toxic phenomena. He advocated a rate of 40 to 60 drops per minute for the introduction of physiological saline or 5 per cent dextrose solution. Following Matas, the next great proponent, in America, of the slow intravenous drip, was Hendon,[22] who estimated that infusions should be paced at a rate of 200 cc. of fluid per hour. He described toxic phenomena arising from rapid introduction as the result of milking the tube. He noted that slow rates of flow eliminated untoward phenomena. He increased the indications for the use of intravenous infusion to include emesis gravidarum, grave icterus, ulcerative colitis, bleeding ulcers, intestinal obstruction and liver abscess. Both Matas and Hendon were concerned with the velocity factor, essentially from the standpoint of the etiology and prevention of untoward reactions.

Despite the clarity of their presentation and the accuracy of their observations on velocity, the work of Matas and Hendon did not obtain

wide currency or acceptance. The importance of velocity in intravenous injection was so little heeded that the Committee on Intravenous Therapy[23] appointed by the American Medical Association, in 1927, had only the following to say concerning rapid injections: "The rapid administration introduces several hazards, (1) the danger of overwhelming the heart and circulation with too great a volume of fluid; (2) the risk of breaking down some compensatory mechanisms as those which maintain the reaction of the blood, its osmotic tension, viscosity and the like within the narrow limits of normality; and (3) the likelihood of carrying the drug in too high concentration." The first hazard referred to the "bulk phenomenon" (v.i.); the second and third statements were unsupported by any clinical or laboratory observations. No mention was made of the observations of Matas and Hendon. No definition of velocity was advanced. The text books on pharmacology, in discussions of intravenous injection, were silent on the effect of velocity, except for Sollmann[10] who in 1927 wrote: "A primary fall in blood pressure is apt to occur with all kinds of intravenous injection ***** [This] has been an annoying complication of experimenters on animals and no less annoying in clinical practice."

In 1929, Keith[24] summarized the literature on the physiological principles and therapeutic applications of intravenous medication. Concerning velocity he wrote: "The rate of injection of intravenous solution is often too rapid. From 30 cc. to 40 cc. each minute is a satisfactory rate when a considerable amount of fluid is being injected." The work of Matas was neither quoted nor mentioned. The toxic phenomena, due to rapid introduction of pharmacologically inert substances, were unnoted. The "satisfactory rate of administration" was ten times that suggested by Matas.

Speed Shock

In 1931, my colleagues and I[15] produced and described "speed shock." We demonstrated that the "rapid intravenous introduction of pharmacologically active or inert chemicals, drugs and biologic fluids may frequently give rise to immediate and far-reaching non-specific sequelae, at times serious, and occasionally fatal." "Speed shock" was produced, in the laboratory, in cats, dogs, rabbits, and monkeys. Both anesthetized and unanesthetized animals were used. Injections were commonly made into the femoral vein. In the unanesthetized animal, the

fluid was introduced through venipuncture. In the anesthetized animals, the vein was usually prepared with a cannula. Amounts of fluid of less than 5 cc. were delivered into the vein or cannula with the greatest possible speed by means of syringe. Larger quantities of fluid were permitted to run in, by gravity, from an ordinary 25 cc. buret. With the buret the rate of speed varied from 3 to 10 cc. per minute. During the experiments, carotid blood pressures were recorded on the kymogram. Usually the respiratory tracing was superimposed. The experiments were planned so that after the animal recovered from the operative procedure, "speed shock" was obtained by rapidly introducing one or two cubic centimeters of the substance under investigation. No attempt was made to resuscitate the shocked animal. If spontaneous recovery ensued, the animal was given a slow infusion of a large amount of the substance that had produced the shock in order to eliminate the possibility that the reaction obtained was specific to the substance, any impurity contained therein, or any imperfection in the apparatus. Following this, "speed shock" was again induced by rapid injection. Each substance was tried on at least three different animals.

The clinical syndrome of "speed shock" occurred 40 to 60 seconds after injection. The symptoms included salivation, vomiting, diarrhea, dyspnea, muscle atony, muscle spasm, or sudden death. Inconstancy and inconsistency in symptomatology were the rule. In fact, it was this irregularity in response that led to the belief that some non-specific variable was the cause of our inability to work out the toxicology and pharmacology of a group of melamins under investigation at the time this work was done.

The most dramatic manifestation of "speed shock" was the rapid and precipitous fall in blood pressure which might be fatal or from which recovery might speedily ensue. Coincident with the circulatory phenomena occurred respiratory distress. There might be simple dyspnea or apnea. At times the lungs collapsed but again, as the result of severe bronchospasm there might be a ballooning of the chest. The circulating blood was rendered non-coagulable. The shock reaction preceded the blood changes.

At autopsy, the lungs were atelectatic or emphysematous. Large fresh thrombi were present in the pulmonary veins. Multiple punctate hemorrhages occurred in the abdominal viscera.

Where recovery followed a "speed shock," less tempestuous changes

could be produced, both in the circulatory and respiratory phenomena, by speeding up or slowing the rate of infusion, confirming a clinical observation of Hendon,[22] who noted these changes as the result of milking the intravenous tube.

The factors that modified "speed shock" seemed to be related to the concentration of the solution and the size of the molecule. Larger molecules and hypertonic solutions more consistently produced shock. It was more difficult to "shock" with viscous substances such as acacia. If a small volume of fluid such as 1 to 2 cc. did not produce shock, a larger amount such as 5 cc. was more likely to be efficacious. The more rapid the injection the more certain the production of "speed shock."

Repeated shocks could be produced with each of the substances studied except sodium bicarbonate and the calcium salts. Occasionally, there was a short period following shock in which the reaction could not be obtained but certainly there was nothing suggesting significant immunity. The simultaneous use, in another vein, of an infusion of acacia made it more difficult to produce shock with any given substance. This protection was not absolute.

There was apparently no species idiosyncrasy in "speed shock" for the reaction could be obtained in cats, dogs, monkeys, and man. Morphine and the anesthetics were unimportant factors since the syndrome was produced in unanesthetized animals. Pyrogenic substances in the diluents could be excluded as the sole factor since slow infusions of each shock substance could be performed with impunity. Shock could be produced equally well whether blood pressure was at a normal or subnormal level. The thermal factor was insignificant, for identical reactions occurred whether the fluids injected were ice cold or warmed to body temperature. The role of protein split products was investigated by subjecting fluids to dialysis. Dialysates reacted identically with the whole product or the bag residue.

The Slow Intravenous Drip

The obvious antidote to "speed shock" was the slow infusion or "intravenous drip." In the clinic there was considerable variation in the definition of what constituted slow injection. Keith[24] employed 30 to 40 cc. per minute as a "satisfactory rate of injection" for dextrose. Osborne,[25] in his text book, defined injection of one quart in 30 minutes, or 30 cc. per minute as a slow injection. The Committee on Intravenous

Therapy[23] of the Council of Pharmacy of the American Medical Association quoted the workers at the Mayo Clinic, who regarded 10 to 20 cc. per minute as a slow rate of injection for water, salt and dextrose. Matas,[21] Hendon,[22] Titus,[26] and Friedman[17] employed rates of 2 to 5 cc. per minute. The clinical concept of slow intravenous injection, therefore, included a range of from 2 to 40 cc. per minute. In the laboratory, on experimental animals, Hanzlik and Karsner[27] advocated a rate of 3 cc. per minute.

Reversing the experiments used in the production of "speed shock," an attempt was made to introduce all of the tested substances in such velocity as not to cause significant circulatory or respiratory reaction. No one rate was applicable to all substances. Powerful drugs could not be given at the same rate as physiological salt solution. Hypertonic solutions had to be given more slowly than isotonic solutions and large molecules more slowly than small molecules. Highly toxic substances such as copper sulphate had to be given intermittently as well as slowly. The findings suggested a rate of 1 cc. per minute as a standard in pharmacologic assay. For clinical purposes, the rate, described by Matas[21] and Hendon,[22] of 2 to 4 cc. per minute seemed the upper limit for amounts of 100 cc. or more and 1 cc. per minute for smaller amounts, particularly if the fluid was a potent biologic substance, such as a serum or a powerful drug. If "speed shock" should prove to be the preponderant cause of the untoward phenomena that accompany or follow intravenous injection, the slow intravenous drip should abolish these irregular and mysterious symptoms as well as "anaphylactoid," "nitritoid" and hemoclastic crises, post-transfusion reactions (not due to incompatibility), peptone shock, acute dilatation of the heart, and sudden deaths that occasionally follow intravenous medication.

The Therapeutic Uses of the Intravenous Drip

The intravenous drip was immediately utilized in the management of a large variety of conditions. These include:

1. The relief of tissue hypohydration
2. The restoration and maintenance of the volume of the circulating fluid
3. As a method of increasing blood viscosity
4. As a means of dehydrating certain specific tissues by the exhibition of hypertonic solutions

5. For the restoration and maintenance of corpuscular volume
6. To supply the metabolic needs of the tissues in general
7. For the introduction of immune substances
8. For the immediate introduction of pharmacologic agencies
9. As a prophylactic and supportive in surgical procedures
10. As a convenient form of therapy for postoperative complications
11. In the medical management of hemorrhagic conditions, shock and metabolic disorders (Hyman and Hirshfeld,[42] Hyman and Touroff[43]).

Intravenous Drip Chemotherapy

The technique of the intravenous drip has opened a new chapter in chemotherapy. The concept of "speed shock" gave rise to the suspicion that the untoward reactions occurring in chemotherapy might not be specific to the drug but technical in their origin. The goal of the chemotherapist had never been achieved, due to the serious and even fatal phenomena that resulted from effective doses of agents such as the arsenicals in syphilis. These untoward reactions resulted either in the abandonment of the chemotherapeutic approach or, as in the treatment of syphilis, in the use of divided doses spread over a period of months or even years.

If the concept of "speed shock" were correct and the immediate toxic effects that followed the introduction of chemotherapeutic agents were technical rather than pharmacological, potent therapeutic agents might be administered "in doses far greater than at present employed, and this without serious damage to the cells of the host."[15] Abolition, by the intravenous drip, of the immediate toxicological phenomena might result in an approach to the goal of massive sterilization. These concepts have reached practical fruition in studies with the sulphonamides and the arsenicals.

Intravenous Chemotherapy with Sulfonamide Derivatives

The introduction of the newer sulfonamides has increased interest in chemotherapy. In the vast majority of patients effective sulfonamide therapy can be maintained by oral administration. Parenteral or intravenous injection is reserved for: (1) patients who are moribund or uncoöperative; (2) those with fulminating infection in whom a high blood level must be rapidly obtained; (3) patients who are so disturbed

by the emesis common to the administration of these drugs that the oral administration must be discontinued; (4) those rare instances where an effective blood level cannot be reached despite adequate oral dosage. Clinical studies employing intravenous sulfonamide, particularly in pneumonia, have been reported by Marshall and Long,[28] Sadusk and Blake.[29]

The intravenous injection of sulfonamides may be accomplished with a small volume of a highly concentrated solution or a continuous intravenous drip of a dilute solution. The former plan has many disadvantages. It requires repeated injections. The concentrated solutions are usually locally irritating. The blood concentration that is produced by repeated injection is rapidly attained and equally rapid in its decline.

The intravenous drip method of chemotherapy is to be highly recommended in the use of sulfonamides. Sulfanilamide, itself, may be given in 0.8 per cent, sodium sulfapyridine and sodium sulfathiazole in 5 per cent concentration.

In unpublished work performed on the Service of Max Pinner at the Montefiore Hospital, Gary Zucker[30] has initiated some interesting observations concerning intravenous drip chemotherapy with sulfanilamide.

Using an 0.8 per cent solution in isotonic sodium lactate, 1200 to 1600 cc., containing 10 to 15 grams of the drug, were injected between 9 A.M. and 7 P.M. The blood level, which could be made to vary with the rate of injection and the total amount administered, reached 16 to 26 mgm. per cent within four hours. This concentration could be maintained until the infusion terminated. In the morning when the drip was again set up, after a lapse of approximately twelve hours, the level was still at 10 mgm. per cent. In the course of five days patients received approximately 60 grams of the drug intravenously. Only a very small percentage of the sulfanilamide was acetylated, the largest portion, perhaps 85 to 90 per cent, circulating as the effectual free form. These concentration curves follow closely those prepared by Sobotka for blood arsenic in massive dose chemotherapy of syphilis.

This high concentration was maintained without marked objective toxicology though subjectively the patient suffered considerably from the familiar cerebral manifestations. Blood counts showed a fall of hemoglobin of 10 to 20 per cent. The urine revealed crystals but was free from manifestations of kidney irritation.

The easy assimilation of these drugs enterally has overshadowed the results of intravenous use. Whether more can be accomplished clinically with the sulfonamides by the maintenance of these higher levels of concentration remains yet to be seen.

In exigencies where specific serum is available, as in pneumococcus pneumonia, the drip may deliver alternately the chemotherapeutic or the specific serotherapeutic agency.

Intravenous Arsenotherapy

The bulk of our experience in massive dose intravenous drip chemotherapy has been with arsenicals in the treatment of primary and secondary syphilis. Since 1931, with Louis Chargin and William Leifer,[31, 32, 33, 34, 35] more than four hundred patients have been treated. Over a span of five days neoarsphenamine has been given in 4 gm. doses, Mapharsen up to 1200 mg. doses. The toxic phenomena and the therapeutic efficacy may now be compared with the results of routine therapy.

The Toxic Phenomena. The first consideration in chemotherapy is concerned with risk. In clinical medicine the patients whose life is not in immediate jeopardy must not be exposed to hazardous therapy *(noli nocere)*. How then does the toxicology of massive dose arsenotherapy compare with that experienced in routine treatment?

Mild and grave toxic phenomena result from all types of arsenotherapy. Of the mild phenomena, to be considered only for their nuisance value, are encountered primary and secondary fever, toxicodermata, an occasional instance of transitory jaundice, and gastrointestinal distress (nausea and vomiting).

The primary fever, occurring on the first day of treatment and lasting but a few hours, has been present in 62 per cent of the patients receiving neoarsphenamine—41 per cent of those in the Mapharsen series. How commonly this occurs in routine therapy cannot be estimated. Moore[36] uses the word, "usually." In the routine ambulatory clinic, where the patient is sent home following the injection, there seems to be no way of estimating the frequency of primary fever. Parenthetically, it may be said in this place that one of the grievous short-comings of the literature of the syphilologists is the paucity of information concerning untoward symptomatology. The published information is sketchy, to say the best. There are wide discrepancies

between the statements of the most eminent workers in this field.

The secondary fever, usually associated with toxicodermata (clearly to be differentiated from the ominous dermatitis exfoliativa) occurred toward the end of treatment in 64 per cent of the patients in the neoarsphenamine group and 12 per cent of those receiving Mapharsen. The occurrence of this complication in routine therapy is not stated.

Renal damage did not occur in any patient. There were daily urine examinations and estimations of renal function by all available methods before and after treatment. Stokes[37] states that renal damage occurred in 10.7 per cent of those receiving routine treatment.

Mild transitory jaundice was seen in 3.6 per cent of the neoarsphenamine series—0.7 per cent of the Mapharsen group. Tests of liver function were done by Louis J. Soffer before and after treatment. The urine was examined daily for urobilin. Moore[36] states that jaundice is "fairly frequent" in routine therapy.

As to nitritoid crises, there were none. Moore[36] places their incidence as 0.1 to 0.5 per cent. According to Stokes,[37] they occur in 20.8 per cent.

Grave Toxic Phenomena. Of the grave toxic phenomena in skin, blood and liver, there was a single instance of dermatitis exfoliativa with recovery. Even this complication was questionable since the patient also received sulfanilamide for a subsequent gonorrheal infection. With this exception there has not been experienced any severe dermatosis, any of the blood dyscrasias such as aplastic anemia or granulopenia, any degenerative hepatitis or nephritis. In routine treatment, Moore[36] states that dermatitis exfoliativa occurs 1/126 with arsphenamine—1/197 with neoarsphenamine. Stokes[37] gives a "fraction of a per cent" for blood dyscrasias. Moore[36] has experienced hepatitis with arsphenamine 1/117, with neoarsphenamine 1/282. If these three complications did not each occur in the same patient the incidence of their presence in the patients treated routinely, according to the Moore figures, must be between 1 and 2 per cent. Since these complications result fatally in more than half of the sufferers, it would indicate an expected treatment mortality for routine therapy approximating 1 per cent.

Peripheral neuritis occurred in 35 per cent of the patients who received neoarsphenamine and 1 per cent of those treated with Mapharsen. Vitamin B and C did not affect the incidence or severity of the neuritis. In the Mapharsen series the neuritis was mild. In no instance

was it incapacitating. In routine therapy peripheral neuritis is "fairly frequent."

The single important toxic phenomenon of grave significance experienced in massive dose chemotherapy has been hemorrhagic encephalitis. Cerebral symptoms have occurred in just short of 2 per cent of the patients. Twice the complication was exceedingly grave; one of the men was unconscious for several days; the other died.

In routine therapy there is a diversity of opinion concerning the incidence of hemorrhagic encephalitis. Moore[36] in 15,000 patients has never seen it. Schamberg[38] reports its incidence "many times." Cole[39] experienced fatal hemorrhagic encephalitis once per two hundred patients. It is his opinion that it causes 62 per cent of all treatment deaths.

Hemorrhagic encephalitis is not produced by overdosage. It occurs as an idiosyncrasy and in routine treatment usually follows a second or third injection. In addition to its incidence in fatal cases, it must occur also in individuals who recover. We can obtain no data on this point from the syphilologists.

Hemorrhagic encephalitis is the greatest threat in massive dose chemotherapy. It is a manifestation of idiosyncrasy, not overdosage. It has been experienced by most syphilologists in routine therapy as frequently as in our series. Moore's experience is apparently unique and beyond our understanding. One hundred per cent of our complications are reported. Is this equally true of routine therapy where patients are ambulatory and the case loss averages 84 per cent?

In our experience, "treatment death" has occurred once in more than four hundred experiences (0.25 per cent). There has been no death in the Mapharsen group. In routine therapy, Cole[39] had twelve treatment deaths, 1 per cent in a series of 1212 patients. More than half of these, approximately a half of 1 per cent, resulted from hemorrhagic encephalitis. Stokes,[37] as well as Phelps[40] in the Navy, has had one treatment death per five thousand to seven thousand injections. If each patient received approximately twenty-five injections, the ratio of treatment death is one to three hundred, or one to four hundred. In comparison, treatment death of 1 per cent in our neoarsphenamine series is but slightly excessive. The mortality of 0.25 per cent in the whole series parallels the routine experience. The record of no treatment death in the Mapharsen series speaks for the relative safety of massive dose chemotherapy.

The Results of Treatment from the Public Health Standpoint

The benefits of massive dose chemotherapy may be discussed with regard, first, to the public health aspects and, second, from the standpoint of the individual patient.

With massive dose chemotherapy, the patient is institutionalized for seven days and receives active treatment for five days. No institutionalization is required for routine therapy.

With massive dose chemotherapy, no ambulatory treatment is required other than for follow-up purposes. Routine treatment means weekly visits at a highly organized clinic.

The infectivity of the patient under routine therapy is three weeks, during which time he mingles with the community. Our patients are dark field negative by the end of forty-eight hours in the hospital. At no time after their discharge do they menace their contacts.

One hundred per cent of our patients complete treatment. If they are lost from follow-up they have exactly the same chance for a satisfactory result as those who have been faithful. In routine therapy, The Cooperative Clinical Group,[41] reporting under the auspices of the United States Public Health Service, state that in their six clinics, including that of Johns Hopkins Hospital from which Moore reports, there was an 84 per cent case loss. Stated positively, sixteen patients in one hundred receive what the group believes to be adequate treatment.

The Results in Terms of the Individual Patient

The results of massive dose arsenotherapy from the standpoint of the individual patient have been reported, under the auspices of the distinguished Committee that has supervised the work.

The first series of twenty-five patients receiving neoarsphenamine was treated at The Mt. Sinai Hospital on the Services of George Baehr in 1933. The immediate results appeared in 1935 and the five-year results in 1939.

The second neoarsphenamine series, now under the direction of the Committee, is approaching a span of observation averaging three years.

The third series of patients received Mapharsen in insufficient dosage. At first 400 mgm. were employed. Tentatively and cautiously, the dosage was worked up to 1200 mgm., the amount that is now considered optimal. An average of 700 mgm. of Mapharsen was given in this series. Series three has been followed for approximately eighteen months.

The fourth group of patients received 1200 mgm. of Mapharsen. The results of therapy in this category are to be compared with the results in the neoarsphenamine series. The results are still incomplete, since the last patient was treated less than six months ago. I am at liberty today to discuss only those results published by our Committee as read at the meeting held at The Mt. Sinai Hospital, in April, 1940.

Re-treatment

In none of the four series was any adjuvant treatment with bismuth or mercury administered. This was not done because of lack of confidence in these drugs. Their administration was omitted in order that a relatively pure clinical experiment might be conducted. In the neoarsphenamine series the patients were not re-treated. It was understood that the results would stand or fall on the basis of the single course. In the small-dose Mapharsen series it soon became obvious that our original dosage was insufficient. Rather than sacrifice the welfare of the patient to the experiment, the policy of re-treatment was instituted. Approximately 10 per cent in this group required second courses. In the large dose Mapharsen series the number of re-treatments has been reduced to 4 per cent. Several of the patients who picked up fresh infections were also re-treated by massive dose arsenotherapy.

Patients who were re-treated were reclassified according to their individual progress.

The Clinical Results of Massive Dose Arsenotherapy

The clinical results are reported in four groups: (1) Patients who were *lost* from observation; (2) those whose reports might be *pending* or *incomplete;* (3) unqualified *failure;* and (4) *satisfactory*. The word "cure" has never been used in any report.

Loss: The case loss in all three groups is 10 per cent. Each of these patients completed treatment. Each has a chance for successful outcome equal to that of those faithful in the follow-up. Since the records are inadequate, the percentage figures noted below exclude the lost cases. In making comparisons with patients treated in routine fashion, it must again be recalled that the Cooperative Clinical Group has a case loss of 84 per cent, none of whom received what is regarded as an adequate amount of therapy.

Pending: In each of our groups, certain patients have been classified

as pending since their records are incomplete. There are 4 per cent in the neoarsphenamine series; 6 per cent in the small dose Mapharsen series; and 21 per cent in the more recent Mapharsen group, many of whose records are soon to be completed satisfactorily.

Failure

Unqualified failures have occurred in all three groups. These patients have had either: (1) an infectious relapse at the site of the chancre; or (2), without clinical symptomatology, they exhibited serum fastness; or (3), serologic relapse. Late syphilis of the central nervous system or the cardiovascular apparatus has yet to be seen. Any lesion other than that at the site of the original sore has not been observed.

Spinal fluid examinations have been made almost without exception. There was but one positive test, and that in a morphine addict with a syphilitic wife.

Satisfactory Result

A satisfactory clinical result is reported in patients who have no clinical symptoms and who have repeatedly and persistently negative serologic reactions by the Wassermann, Kolmer, Kline and Kahn techniques. This has been the outcome in 91 per cent of the neoarsphenamine group; 86 per cent of the small dose Mapharsen group (with 6 per cent still pending): and 78 per cent of the large dose Mapharsen group (with 21 per cent still pending). Nineteen patients were re-treated when their progress appeared unsatisfactory at the crucial period between the tenth and sixteenth week. Fifteen were in the small dose series, and but four in the optimum dose group. Following the second courses, the results could be reclassified as satisfactory.

In the analysis of the satisfactory group, it is particularly to be noted that it contained almost every patient whose infection was of a duration of eight weeks or less. The unsuccessfully treated patients were recruited entirely from those whose infection was of a duration of more than eight weeks.

Comparison With Results of Routine Therapy

What are the results of routine therapy in comparable cases? The figures to be presented make difficult any satisfactory comparison. Firstly, those presented by the Cooperative Clinical Group are from series in

which there is an acknowledged 84 per cent case loss. It is not stated whether the published statistics are based on the number of patients who instituted therapy or those that received adequate therapy. If it is on the basis of those who instituted therapy, and 84 per cent were lost, then only 16 per cent can possibly have had a satisfactory result if every one was cured. On the other hand, if the figures are given as the results in those patients who successfully completed therapy, then comparison with our results is unfair since 100 per cent of our patients completed therapy whether or not they were followed.

Mindful of these possible errors in calculation, four sets of routine figures will be given.

Moore reports, in 1423 patients with early syphilis, that he had 8 per cent failure, and 92 per cent serologic reversal. In his text book[36] he reports on a second group, comparable with ours, with primary sero-negative, primary sero-positive and early secondary syphilis. There were 52 per cent who became serologically cleared and 48 per cent whose course was unfavorable.

Stokes,[37] treating 606 patients by continuous treatment, had 86.8 per cent clearing and 13.2 per cent unfavorable. In a second series of 306 patients, with partly continuous and partly intermittent treatment, there was clearing in 59.4 per cent and 40.6 per cent unfavorable.

The individual results of massive dose arsenotherapy in early syphilis, as compared with those obtained in routine therapy, may conservatively be said to equal the best reported, and far transcend those following less than optimal therapy under less than optimal conditions. If the comparison could be made on the basis of the results in consecutive series of patients initiating therapy, it is highly probable that the satisfactory results in massive dose arsenotherapy would so far exceed those obtained in routine therapy as to outweigh all other considerations, even those voiced by the most captious.

Conclusions

Intravenous drip chemotherapy provides for the direct delivery of relatively massive doses of potent therapeutic agents such as the sulfonamides and the arsenicals. By this means effective concentrations may be produced and maintained without the hazard of the immediate toxic phenomena of "speed shock." Contrary to the expectancy, there do not appear late toxic complications resulting from excessive dosage

or cumulation. Difficulties due to idiosyncrasy crop up unexpectedly, causing treatment morbidity and treatment mortality. The incidence of these closely approximates those of routine therapy. The results of therapy approach the goal of the chemotherapist. They would seem to justify the hazards of increased toxicology, were these present. Richer and wider experience with intravenous drip chemotherapy, using other available preparations in diverse clinical infections, should offer greater hope and a broader horizon in the struggle for the relief of human suffering.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

NOVEMBER 7—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes; b] Report of Nominating Committee. ¶ Papers of the evening—New knowledge of vitamins B and K—a] Vitamin B complex, Norman Jolliffe, Associate Professor of Medicine, New York University College of Medicine; b] Vitamin K, William DeWitt Andrus, Associate Professor of Surgery, Cornell University Medical College. ¶ Report on election of Fellows.

NOVEMBER 28—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The Second Harvey Lecture, "Thrombosis and the Action of Heparin," Charles H. Best, Professor of Physiology, University of Toronto.

DECEMBER 5—*The New York Academy of Medicine.* Executive session—a] Reading of the minutes; b] Report of Nominating Committee; c] Election of Academy officers. ¶ Papers of the evening—Newer knowledge of liver disease—a] Surgical aspects, I. S. Ravdin, George Lieb Harrison Professor of Surgery, University of Pennsylvania, School of Medicine; b] Evaluation of laboratory methods, Alexander B. Gutman, Assistant Physician, Presbyterian Hospital; c] Clinical methods, Franklin M. Hanger, Associate Physician, Presbyterian Hospital. ¶ Report on election of Fellows.

DECEMBER 19—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The Third Harvey Lecture, "The Electrolytes of Tissues and Body Fluids," A. Baird Hastings, Professor of Biological Chemistry, Harvard Medical School.

SECTION MEETINGS

NOVEMBER 1—*Surgery.* Reading of the minutes. ¶ Presentation of cases—a] Case report of bilateral ligation of internal and external carotid arteries for cerebral arteriovenous aneurysm, Bronson S. Ray; b] Five cases of osteomyelitis of the cranial vault, Joseph E. J. King; Discussion by Frederick M. Law. ¶ Papers of the evening—a] Myeloscopy: Endoscopic diagnosis of conditions affecting the cauda equina and lower spinal cord, James Lawrence Pool (by invitation); b] Surgical treatment of paralysis agitans (moving picture illustrations), Tracy J. Putnam. ¶ General discussion. ¶ Executive session.

NOVEMBER 6—*Dermatology and Syphilology.* Presentation of cases—a] Mt. Sinai Hospital; b] Miscellaneous cases. ¶—a] Eulogium—Wm. A. Pusey, Howard Fox; b] Eulogium—Ludwig Oulmann, Herman Goodman. ¶ General discussion. ¶ Executive session.

NOVEMBER 12—*Combined Meeting, Section of Neurology and Psychiatry and the New York Neurological Society.* Reading of the minutes. ¶ Presentation of case—a] Amyotrophic lateral sclerosis treated with synthetic vitamin E, I. S. Wechsler. ¶ Papers of the evening—a] Changes in cerebral blood-flow and arterio-venous oxygen difference during insulin hypoglycemia, H. E. Himwich (by invitation), K. M. Bowman, C. Daly (by invitation), Mr. J. F. Fazekas (by invitation), J. Wortis (by invitation), W. Goldfarb (by invitation); Discussion by Tracy J. Putnam, Ephraim Shorr; b] Studies on pain; nature of pain due to local cooling and the mechanism of its production, Stewart G. Wolf (by invitation), J. D. Hardy, Ph.D. (by invitation); Discussion by Harold Wolff, William Bierman. ¶ General discussion.

NOVEMBER 13—*Historical and Cultural Medicine.* Reading of the minutes. ¶ Papers of the evening—a] The evolution of clinical sphygmomanometry, William Hall Lewis, Jr.; Discussion by Lewis

Fox Frissell, Charles J. Brin (by invitation), Edward H. Hume; b] Illustrious figures in Chinese medicine, Edward Hicks Hume; Discussion by Professor Cyrus H. Peake (by invitation). ¶ General discussion.

NOVEMBER 14—*Pediatrics.* Residents' program. Reading of the minutes. ¶ Papers of the evening—a] New York Hospital, Endocarditis due to a fusiform bacillus, Martin J. Glynn (by invitation); Discussion, Samuel Z. Levine; b] New York Post-Graduate Medical School and Hospital, Sickle cell anemia in a white family, Francis C. DeLorenzo (by invitation); Discussion, Marshall C. Pease; c] Long Island College of Medicine, Erythroblastosis fetalis in dissimilar twins associated with a severe maternal anemia and hypoproteinemia, Peter A. Perillo (by invitation); d] Harlem Hospital, Parke-Weber-Dimitri disease (cerebral telangiectasis), Maurice M. Kay (by invitation); e] Babies' Hospital, Acute episodes in glycogen disease, Richard G. Hodges (by invitation); Discussion by Howard H. Mason; f] Flower and Fifth Avenue Hospitals, An undiagnosed case with a septic temperature of six months duration and a bizarre clinical picture, Sydney H. Gurian (by invitation); g] Lincoln Hospital, Staphylococcus septicemia with recovery in a three-year-old child, Edward Press (by invitation); Discussion by Harry S. Altman; h] Mount Sinai Hospital, Pneumococcus meningitis: recovery in an infant aged ten months, Arnold Widerman (by invitation); Discussion by Bela Schick.

Orthopedic Surgery—Instead of the regular meeting at the Academy of Medicine, the Section of Orthopedic Surgery met on November 15 with the Philadelphia Orthopedic Club in Philadelphia.

NOVEMBER 18—*Ophthalmology.* Exhibits—a] Comparative anatomy of the eye, Army Medical Museum, Lt. Col. J. E. Ash, Washington, D. C. (by invitation); b] Stereoscopic drawings of ophthalmologic neuro-anatomy, P. J. Leinfelder, Lee Allen, Iowa City, Iowa (by invitation); c] Mammalian fundi, LeGrand Hardy; d] Normal variations of the optic canals, Raymond L. Pfeifer. ¶ Reading of the minutes. ¶ In memoriam—Dr. Ben Witt Key, Samuel Oast. ¶ Papers of the evening—The clinical aspects of anatomy; a] The orbit, Raynold N. Berke, Hackensack (by invitation); b] The central nervous system with particular regard to the visual pathway and the oculo-motor system, George A. Blakeslee; c] The eyeball, F. Bruce Fralick, Ann Arbor (by invitation). ¶ General discussion.

NOVEMBER 19—*Medicine.* Reading of the minutes. ¶ Papers of the evening—a] Medical approach to the cancer problem, Cornelius P. Rhoads; b] Diagnosis and treatment of diseases of the lymph nodes, Francis Carter Wood; Discussion by James Ewing. ¶ General discussion. ¶ Executive session.

NOVEMBER 20—*Otolaryngology.* Reading of the minutes. ¶ Papers of the evening—a] Surgical aspects of carcinoma of the larynx, John D. Kernan; b] Roentgenotherapy of cancer of the larynx and pharynx, Maurice Lenz. ¶ General discussion.

NOVEMBER 20—*Genito-Urinary Surgery.* Reading of the minutes. ¶ Papers of the evening—Symposium on the management of genito-urinary malignancies—a] Malignancies of the prostate, Lloyd Lewis, Johns Hopkins University, Baltimore (by invitation); b] Malignancies of the urinary bladder, Ernest M. Watson, Buffalo (by invitation); c] Malignancies of the kidney, Henry G. Bugbee. ¶ Discussion opened by—a] Roy B. Henline; b] Nathaniel P. Rathbun; c] Fedor L. Senger. ¶ General discussion. ¶ Executive session.

NOVEMBER 26—*Obstetrics and Gynecology.* Reading of the minutes. ¶ Papers of the evening—Program by the Lying-in Department of New York Hospital. ¶ Physiology of pregnancy—a] Hormones, Herbert F. Traut; b] Vitamins, Carl T. Javert (by invitation); c] Urinary tract, Charles M. McLane (by invitation);

d] Metabolism, A. T. Milhorat (by invitation); e] Diet, R. Gordon Douglas (by invitation), Ralph C. Benson (by invitation); Discussion by Alfred C. Beck.

DECEMBER 3—*Dermatology and Syphilology.* Presentation of cases—a] New York University College of Medicine and Bellevue Hospital; b] Miscellaneous cases. ¶ Discussion of cases. ¶ Executive session.

DECEMBER 6—*Surgery.* Reading of the minutes. ¶ Presentation of cases—a] From the Babies Hospital—1. Diaphragmatic hernia; 2. Ligation of patent ductus arteriosus (3 cases); 3. Bleeding Meckel's diverticulum; 4. Gangrenous intussusception; Discussion by E. J. Donovan; b] Case illustrating paper of evening, Percy Klingenstein. ¶ Papers of the evening—a] Meckel's diverticulum in infancy and childhood, Percy Klingenstein; Discussion by Edward H. Peterson; b] Acute abdominal conditions in children, Charles W. Lester; Discussion by Charles E. Farr. ¶ General Discussion.

DECEMBER 10—*Neurology and Psychiatry.* Reading of the minutes. ¶ Papers of the evening—a] Spontaneous occlusion of the common carotid artery, Morton Galdston (by invitation), Sidney Govons (by invitation), S. Bernard Wortis; Discussion by J. Murray Steele, Henry K. Taylor; b] Further results of vitamin B_6 therapy in paralysis agitans, Norman Jolliffe; Discussion by Josephine Neal; c] Electro-encephalographic changes during hyper-ventilation in epileptic and non-epileptic disorders, Norman Q. Brill (by invitation), Herta Seidemann (by invitation); Discussion by Richard M. Brickner, Paul F. A. Hoefer (by invitation); d] The human electrocorticogram. A study of electrical potentials taken directly from the exposed brain in health and in disease, John E. Scarff, Mr. Walter E. Rahm (by invitation); Discussion by Tracy J. Putnam, S. Eugene Barrera (by invitation).

DECEMBER 12—*Pediatrics.* Reading of the minutes. ¶ Papers of the evening—a] Emphysema: A dominant finding in an acute respiratory infection, Margaret R. Reynolds; Discussion by Marshall C. Pease; b] So-called essential hypertension in childhood, Irwin Philip Sobel; Discussion by Maurice Bruger (by invitation), Henry A. Schroeder (by invitation), John D. Lyttle; c] The normal development of the male genitalia and secondary sex characteristics from birth through puberty, William A. Schonfeld (by invitation); Discussion by Hilde Bruch (by invitation), Harry H. Gordon (by invitation). ¶ Showing of film—"When Bobby goes to school."

DECEMBER 16—*Ophthalmology.* Demonstration of cases. ¶ Exhibits of new ophthalmological instruments by various firms. ¶ Reading of the minutes. ¶ Presentation of cases—a] A case of intra-epithelial epithelioma of the cornea, John S. McGavic (by invitation); b] A case of lattice keratitis, W. Guernsey Frey, Jr.; c] A case of symmetrical bilateral coloboma of the iris, lens, retina, and choroid, Martin H. Kilmann (by invitation); d] A case of cystic pterygium operated successfully by a new technique, William B. Doherty; e] Three cases of episcleritis in rheumatoid arthritis, Jules W. Smoleroff (by invitation); f] A case of malignant teratoma of the orbit, Albert V. Saradarian (by invitation); g] A case of Boeck's sarcoid, Jesse M. Levitt (by invitation). ¶ Papers of the evening—a] Capsulotomy and iridocapsulotomy technique with a special keratome and iridocapsulotomy scissors, Conrad Berens; b] The mechanics of optic nerve traction upon the retina during ocular rotation, with special reference to retinal detachment, Benjamin Friedman.

DECEMBER 17—*Medicine.* Reading of the minutes. ¶ Presentation of cases—a] Measurement of the pain threshold; a new approach to the study of pain, James D. Hardy (by invitation); b] Measurement of the pain threshold; the effect of analgesics, Harold G. Wolff; Discussion by McKeen Cattell, Harry Gold; c] The

significance of muscular weakness in Graves' disease (with moving pictures), Ephraim Shorr (by invitation); Discussion by Ade T. Milhorat (by invitation). ¶ General discussion. ¶ Executive session.

DECEMBER 17—*Obstetrics and Gynecology.* Reading of the minutes. ¶ Papers of the evening—a] The pulse and respiratory rate during labor, Curtis L. Mendelson (by invitation); Discussion by Harold E. B. Pardee; b] Cause and prevention of transfusion accidents in pregnancy, Philip Levine, Eugene M. Katzen; Discussion by Reuben Ottenberg, Lyman Burnham (by invitation).

DECEMBER 18—*Otolaryngology.* Reading of the minutes. ¶ Reports of cases—a] Hemangioma of the nasal cavity with persistent, severe hemorrhage, cured by radium therapy, Samuel Morse (by invitation); Discussion by W. Wallace Morrison; b] Type III pneumococcus meningitis and septicemia with complete recovery, M. Moghtader (by invitation). ¶ Papers of the evening—a] Sulfanilamide in otitis media in children, Edwin Bilchick, George H. O'Kane (by invitation); b] Tonsillectomy with conservation of tissues, fascia and mucosa, Robert H. Fowler.

DECEMBER 18—*Genito-Urinary Surgery.* Reading of the minutes. ¶ Papers of the evening—Symposium on non-specific infections of the genito-urinary tract (excluding gonorrhea and tuberculosis)—a] Chemotherapy in urinary tract infections, Edwin P. Alyea, Durham, North Carolina (by invitation); b] The formation of urinary calculi produced by the Proteus ammoniae, C. Donald Creevy, Minneapolis (by invitation). ¶ Discussion by Meredith Campbell. ¶ General discussion. ¶ Executive session.

DECEMBER 20—*Orthopedic Surgery.* Reading of the minutes. ¶ Presentation of cases—a] Fracture through sacroiliac joint associated with nerve injury. End-result following muscle transplantation, Ernest Burgess (by invitation); b] Fracture of the acetabulum followed by limitation of motion of the hip. Acetabuloplasty, Donald Starr (by invitation). ¶ Paper of the evening—Fracture of the pelvis. Anatomical reduction and treatment of complications, F. Walter Carruthers, Little Rock, Arkansas (by invitation). ¶ General discussion by John A. Taylor, Ralph L. Barrett, Samuel A. Jahss (by invitation).

AFFILIATED SOCIETIES

NOVEMBER 18—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Papers of the evening—a] The effect of the shape of the heart on the electrocardiographic pattern, Arthur M. Master (by invitation); b] Contrast visualization of the cardiac chambers in emphysema, Marcy L. Sussman, Morris F. Steinberg (by invitation), Arthur Grishman (by invitation); c] Constructive pericarditis—1. Circulatory dynamics, William M. Hitzig (by invitation); 2. Clinical and roentgen features, Bernard S. Oppenheimer (by invitation); 3. Surgical aspects, Harold Neuhof (by invitation). ¶ Discussion—a] Charles Aden Poindexter (by invitation); b] George P. Robb (by invitation); c] Samuel Olcott Thompson (by invitation). ¶ Executive session.

NOVEMBER 28—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Case report—a] Postpartum necrosis of the pituitary gland, Alfred Plaut, Beth Israel Hospital. ¶ Papers of the evening—a] An experimental study of nutrition and age as factors in the pathogenesis of common diseases of the rat, John A. Saxton, Jr. (by invitation), Cornell University Medical College; b] Relationship of bacteriological procedures to the diagnosis and therapy of pneumonia, Wheelan D. Sutliff (by invitation), Bureau of Laboratories, Department of Health. ¶ Executive session.

DECEMBER 16—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Symposium on arthritis—a] Classification and clinical aspects, Currier McEwen (by invitation); b] Pathological aspects, D. Murray Angevine (by invitation); c] Radiological aspects, Haig H. Kasabach. ¶ Discussion by Edward F. Hartung (by invitation), Ralph H. Boots (by invitation).

DECEMBER 18—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Case Reports—a] Spontaneous non-traumatic rupture of posterior papillary muscle of the heart, Caspar Burn, Kings County Hospital; b] Carcinoma of the stomach with skeletal metastases, myelophthisic anemia and splenomegaly, M. W. Johannsen, Bellevue Hospital. ¶ Papers of the evening—a] Concerning the etiology of cystic fibrosis of the pancreas, Henry Brody, Beth Israel Hospital; b] Phosphatase in normal and malignant tissues, Jacob Furth, E. A. Kabat (by invitation), Cornell University Medical College. ¶ Executive session.

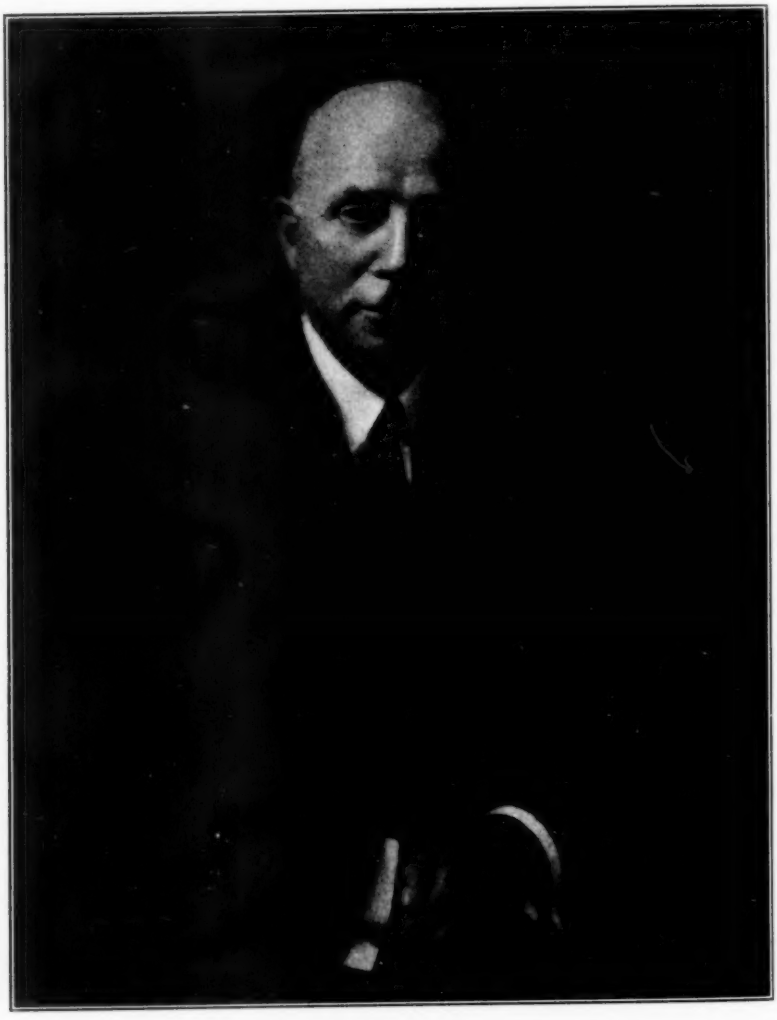
DEATHS OF FELLOWS

HARTWELL, JOHN AUGUSTUS: 1067 Fifth Avenue, New York City; born in Deckertown, County Sussex, New Jersey, September 27, 1869; died in Oakdale, Long Island, New York, November 30, 1940; received the degree of Bachelor of Philosophy from Yale University in 1889 and graduated in medicine from Yale Medical School in 1892; elected a Fellow of the Academy November 7, 1901; served as a member of the Committee on Public Health Relations 1917-1929; as vice-president of the Academy 1918-1920; as president 1929-1932; as a member of the Committee on Medical Education 1933-1934; and as a member of the Board of Trustees in 1928, 1933-1934, and again from 1939 until his death. He was director of the Academy 1934-1939.

Dr. Hartwell was emeritus clinical professor of surgery at Cornell University Medical College and was consulting surgeon to Bellevue, Presbyterian, Reconstruction Unit of Post-Graduate, Memorial and Lincoln Hospitals, the Lawrence Hospital in Bronxville, the United Hospital in Port Chester and the New York Infirmary for Women and Children. In 1939 he became associate director of the American Society for the Control of Cancer.

He was a Fellow of the American College of Surgeons and a member of the New York Surgical Society, the American Surgical Association, the Society of Clinical Surgeons, the American Association for Thoracic Surgery, the American Medical Association and the County and State Medical Societies.

During the World War, Dr. Hartwell served in the Army Medical Corps and was discharged with the rank of Major.



JOHN A. HARTWELL

1869-1940

IN MEMORIAM

John A. Hartwell

In the death of our Ex-President and Ex-Director, John A. Hartwell, the Academy has suffered a very great loss. Captain Liddell Hart in his "Reputations Ten Years After" says of General Gallieni, the real author of the Miracle of the Marne: "but the finest epitaph and that most acceptable surely to him, is also the simplest: 'Gallieni —la tête haute.'" How descriptive of Hartwell! I can imagine no truer motto for him throughout his whole career in athletics, teaching, surgery, and his later executive positions.

My acquaintance with him began as an undergraduate at college where one of my early memories of him is his futile but game pursuit of Lee, who scored a winning touchdown in a Yale-Harvard game. As captain of the famous '92 Crew, which made in June the second fastest record time at New London, he displayed his courage, a dominant trait throughout his life, in the removal against the advice of the coach of a famous powerful, but overweight member of the crew who had also rowed the year before but could not pull his own weight in the boat. Whatever the odds, once his mind was made up that a course of action was desirable "Josh" fought indomitably, sometimes with steam-roller methods, to accomplish his purpose. And he was usually right! Another early recollection is in Professor Chittenden's laboratory, Sheffield Scientific School. I was puzzled in some mathematical calculation when Chittenden finally remarked impatiently: "Josh Hartwell would never have done this, but then he was bright!"

In looking over Dr. Hartwell's vast number of professional appointments, both teaching and hospital, it is difficult to know which to emphasize. Shortly after graduation as Intern he became Instructor and in 1901 Assistant Professor of Physiology at Cornell and then, as natural in one who had come through Chittenden's laboratory, did much research work. His experiments in high intestinal obstruction in dogs and the prolongation of life by large parenteral doses of normal saline is fundamental, and has become the basis of subsequent treatment in humans. On the academic side, in the various grades of Assistant Professor of Surgery, Associate Professor of Surgery, Professor of Clinical Surgery and Professor Emeritus of Surgery at Cornell from 1909 to 1936, he threw the same energy into the instruction of medical youth that distinguished him in his own hospital and private practice. His main hospital interests were at Bellevue to which he became attached in 1903, rising through various grades until in 1916 he became Visiting Surgeon and Director of the 2nd Division and finally Consultant in 1928. Into all this work Dr. Hartwell again threw all of his energy and it was in this period that he organized the Cornell Clinic where patients of moderate means received expert care for a small fee. No one of his appointments gave him more pleasure than his nomination in 1908 to the post of Assistant Surgeon at Presbyterian Hospital, where he had interned. Well do I remember the dinner given at the University Club on this occasion and Josh's delight. This connection lasted until the union of Columbia and Presbyterian Hospital and the consequent withdrawal of the Cornell members from the staff. In all of his hospital and teaching appointments he had something of the attitude which later characterized him in his executive positions, the courage to fight for what he considered right, regardless of opposition. This was ably satirized by Dr. Corwin in his speech at the Academy Dinner on Dr. Hartwell's retirement from the Directorship which described him as a mixture of Don Quixote and Cato. Yet throughout his speech this truth was emphasized; he was essentially a crusader with all the virtues and

vices characteristic of that type of mind. This, however, was qualified by a rare judgment of men and a diplomacy which enabled him to use even those who disagreed with him on details.

During the war he held the rank of major and taught war surgery to surgeons entering the army and was instrumental in standardizing surgical dressings used in the army. In France in 1918-19 he was assigned to duty with the Chief Surgeon of the First Army.

His association with the Academy began with his election as fellow in 1901. He served on the Public Health Committee from 1917 to 1929 and at this time began his acquaintance with public health problems which later, in his Presidency and Directorate, gave him the knowledge to speak with authority before civic and legislative boards. This he did convincingly on many occasions, becoming widely known as the civic, state and, to a lesser extent national, mouthpiece of medical opinion. Here he struck a mean between the extreme liberal and extreme conservative positions. He was particularly interested in the fight against cancer and in 1939 became Associate Director of the American Society for the Control of Cancer. He made frequent appearances before legislative committees in Albany to protest against the enactment of legislation which would prohibit experiments on living dogs. He was a determined opponent of fee-splitting and also directed attention to the dangers of overspecialization and urged that there be more physicians of the type of old-fashioned family doctor who was skilled in all branches of medicine and specialized in none.

As Director of the Academy of Medicine he was faced with the problem of declining revenue and the necessity, in the eyes of many of his associates, of balancing the budget. Full of optimism, which with his invincible courage was perhaps one of his two most distinguishing characteristics, he declined to cut down any of the Academy's activities, insisting that appeals to the public could balance the budget and it was unthinkable that the Academy should curtail any of its Public Health, Medical Education, or Medical Information work. During all of his later years he was crippled much of the time by vascular trouble of the legs, which had plagued him ever since an attack of typhoid phlebitis during his hospital internship. Directing the affairs of the Academy from a hospital bed, or from his oscillating table, and being carried on a stretcher to vote or to a duck blind, he seems here to be carrying out to the full the motto, "La Tête Haute."

Always an ardent sportsman, he was a member of the Board of Directors of "More Game Birds in America" and it was his expressed hope that he might die with a fishing rod or a gun in his hand. In the end death came as his guide handed him his gun on his last duck-shoot.

LEWIS FOX FRISSELL.